EXPLORING THE MANAGEMENT OF PATIENTS WITH CHRONIC LIMB THREATENING ISCHAEMIA DUE TO INFRA-POPLITEAL DISEASE

By

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A Thesis submitted to the University of Birmingham

for the degree of

DOCTOR OF MEDICINE



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September 2021

Word Count 34,95

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ABSTRACT

Introduction

The incidence of chronic limb threatening ischaemia (CLTI) secondary to infra-popliteal (IP) disease is increasing. Despite this, the current evidence base supporting clinical management decisions is poor.

Methods & Aims

To use the vehicle of the Bypass versus Angioplasty in Severe Ischaemia of the Leg 1 and 2 (BASIL-1 and 2) randomised controlled trials to provide new evidence to help inform treatment decisions for patients presenting with CLTI secondary to IP disease.

Results

Both the IP subgroup analysis of BASIL-1 and retrospective analyses of data from our own institution revealed that vein bypass was associated improved overall survival, although patients experienced higher rates of morbidity and longer in hospital stays than those undergoing endovascular treatment. Although immediate technical outcomes have improved in endovascular treatment since BASIL-1, overall survival and limb salvage have not. IP vein bypass and major amputation are more expensive in terms of human resources and in-patient costs. The overall survival of patients with untreated CLTI is poor at around 50% at 1 year.

Conclusions

Evidence from this thesis suggests that IP endovascular treatment should likely be reserved for those who are not suitable for vein bypass, however further randomised trials and a large, concerted, public health effort are required to confirm this and achieve improved outcomes in this challenging patient group.

DEDICATION

The thesis is dedicated to all my family and friends who have supported me throughout my medical education since 2004.

ACKNOWLEDGEMENTS

I would like to acknowledge the help and support that I have received since 2014 when work on this project and thesis started; a special mention to the people listed below.

Professor Andrew Bradbury – For all his guidance, help and opportunity. Coming to work in Birmingham on this project has been transformative for my development and career and I owe a lot of gratitude to the Professor for making all this possible and supporting me since 2014.

Mr Gareth Bate – For all his help and advice with clinical and non-clinical matters, Gareth has been an asset and a friend, and I cannot thank him enough for his help and support with the BASIL trials and with some of the work presented in This Thesis.

Mr Huw Davies – Huw and I were research fellows together during the same period and shared an office for 2 years. His companionship, willingness to help and comradery will never be forgotten, and a lot of this work would not have been possible without his support and friendship.

To all the Vascular Team at Birmingham Heartlands Hospital including consultants, junior colleagues, nursing and support staff, thank you for all your support and help with this project.

Salary to support the period of research culminating in This Thesis was funded through the National Institute for Health Research (NIHR) Health Technology Association (HTA) BASIL-2 trial (ISRCTN27728689).

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LIST OF ABBREVIATIONS

ABPI	Ankle Brachial Pressure Index
AFS	Amputation Free Survival
AKA	Above Knee Amputation
ANOVA	Analysis of Variance
AP	Ankle Pressure
BASIL-1	Bypass versus Angioplasty in Severe Limb Ischaemia of the Leg Trial
BASIL-2	Bypass versus Angioplasty in Severe Limb Ischaemia of the Leg Trial-2
BASIL-3	Balloon versus Stenting in Severe Limb Ischaemia of the Leg Trial – 3
BCTU	Birmingham Clinical Trials Unit
BEST-CLI	Best Endovascular vs. Best Surgical Therapy in Patients with Critical Limb Ischaemia
BET	Best Endovascular Therapy
BKA	Below Knee Amputation
BMS	Bare Metal Stent
BMT	Best Medical Therapy
BP	Blood Pressure
BSX	Bypass Surgery
BS	Bypass Surgery
CAD	Coronary Artery Disease
CC	Complications and Comorbidity
CD	Clavien-Dindo
CG	Clinical Guideline
CI	Confidence Interval
CLI	Critical Limb Ischaemia
CLTI	Chronic Limb Threatening Ischaemia
COMPASS	Cardiovascular Outcomes for People using Anticoagulation Strategies

CONSORT	Consolidated Standards or Reporting Trials
CRF	Case Report Form
CS	Contemporary Series
CTA	Computer Tomography Angiogram
CTO	Chronic Total Occlusion
DCB	Drug Coated Balloon
DES	Drug Eluting Stent
DM	Diabetes Mellitus
DOAC	Direct Oral Anti-Coagulant
DSA	Digital Subtraction Angiography
DUS	Duplex Ultrasonography
EAG	Expert Advisory Group
EBM	Evidence Based Medicine
EBR	Evidence Based Revascularisation
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESRD	End-stage Renal Disease
ESVS	European Society of Vascular Surgery
EVT	Endovascular Treatment
FF-MALE	Freedom from Major Adverse Limb Event
FF-R	Freedom from Re-intervention
FP	Femoro-popliteal
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GIRFT	Getting It Right First Time
GLASS	GLobal Anatomic Staging System
GMC	General Medical Council
GRADE	Grading of Recommendations, Assessment, Development and Evaluations

CS	Contemporary Series
GVG	Global Vascular Guidelines
HDU	High Dependency Unit
HE	Health Economy
HEFT UHB	Heart of England Foundation Trust University Hospitals Birmingham
HES	Hospital Episode Statistics
HR	Hazard Ratio
HRA	Health Research Authority
HRe	Human Resources
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
IC	Intermittent Claudication
ICU	Intensive Care Unit
IDDM	Insulin Dependent Diabetes Mellitus
IDEAL	Idea Development Exploration Assessment Long-term
IHD	Ischaemic Heart Disease
IN.PACT DEEP	Randomised IN.PACT Amphirion Drug-Coated Balloon vs. Standard Percutaneous Transluminal Angioplasty for Treatment of Below-the-Knee Critical Limb Ischaemia Trial
IP	Infrapopliteal
IQR	Inter-quartile range
IR	Interventional Radiologist
ITU	Intensive Care Unit
LA	Local Anaesthetic
LBP	Limb Based Patency
LDL	Low Density Lipoproteins
LMIC	Low Middle Income Countries
LS	Limb Salvage
MACE	Major Adverse Cardiac Event

MALE	Major Adverse Limb Event
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MLLA	Major Lower Limb Amputation
Mg	Milligrams
mmHg	Millimetres of Mercury
MRA	Magnetic Resonance Angiography
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NIHR	National Institute for Health Research
NS	Non-significant
NSAID	Non-steroidal Anti-inflammatory Drugs
NVR	National Vascular Registry
ODP	Operating Department Practitioner
ONS	Office for National Statistics
OR	Odds Ratio
OS	Overall Survival
PAD	Peripheral Arterial Disease
PBA	Plain Balloon Angioplasty
PCS	Prospective Cohort Study
PEDIS	Perfusion, Extent, Depth, Infection, Sensation
PLAn	Patient Risk, Limb Threat and Anatomical severity
PLATO	Platelet Inhibition and patient outcomes study
PSSRU	Personal Social Services Research Unit
PTFE	Polytetrafluoroethylene
PVR	Pulse Volume Recording

QALY	Quality of Life Adjusted Year
QIF	Quality Improvement Framework
QoL	Quality of Life
RCT	Randomised Controlled Trial
REACH	Reduction of Atherothrombosis for Continued Health Registry
RR	Relative Risk
SD	Standard Deviation
SET	Supervised Exercise Therapy
SFA	Superficial Femoral Artery
SLI	Severe Limb Ischaemia
SSI	Surgical Site Infection
SVS	Society for Vascular Surgery
SWEDEPAD	Swedish Drug Elution Trial in Peripheral Arterial Disease
TAP	Target Artery Pathway
TASC	Trans-Atlantic Intersociety Consensus
TBPI	Toe Brachial Pressure Index
TcPO2	Transcutaneous Oxygen Pressure
TIA	Transient Ischaemic Attack
TLR	Target Lesion Revascularisation
TMA	Transmetatarsal Amputation
TP	Tibioperoneal
UK	United Kingdom
US	United States
VAS	Visual Analogue Scale
VB	Vein Bypass
VOYAGER PAD	Vascular Outcomes Study of Aspirin along with Rivaroxaban in Endovascular or Surgical Limb Revascularisation for Peripheral Artery Disease.
VQI	Vascular Quality Initiative

VS	Vascular Surgeon
VSGBI	Vascular Society of Great Britain and Ireland
VSQIP	Vascular Services Quality Initiative Programme
VTE	Venous Thrombo-embolism
WFVS	World Federation of Vascular Societies
WIfI	Wound Ischaemia Foot infection
WM	West Midlands

LIST OF PUBLICATIONS ARISING FROM THIS THESIS

I. Popplewell MA, Davies H, Jarrett H, Bate G, Grant M, Patel S, Mehta S, Andronis L, Roberts T, Deeks J, Bradbury A; BASIL-2 trial investigators. Bypass versus angioplasty in severe ischaemia of the leg -2 (BASIL-2) trial: study protocol for a randomised controlled trial. *Trials*. 2016; 17:11.

II. Popplewell MA, Davies HOB, Narayanswami J, Renton M, Sharp A, Bate G, Patel S, Deeks J, Bradbury AW. A Comparison of Outcomes in Patients with Infrapopliteal Disease Randomised to Vein Bypass or Plain Balloon Angioplasty in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg (BASIL) trial. *Eur J Vasc Endovasc Surg.* 2017; 54:195-201.

III. Popplewell MA, Davies HOB, Renton M, Bate G, Patel S, Deeks J, Bradbury AW. Comparison of outcomes following infrapopliteal plain balloon angioplasty in the BASIL trial (1999-2004) and in a contemporary series (2009-2013). *Vasc Endovascular Surg*. 2020; 54(2):141-146.

IV. Popplewell MA, Davies HOB, Meecham L, Bate G, Bradbury AW. Comparison of Clinical Outcomes in Patients Selected for Infra-Popliteal Bypass or Plain Balloon Angioplasty for Chronic Limb Threatening Ischaemia Between 2009 and 2013. *Vasc Endovascular Surg*. 2020; 55(1): 1538574420953949. (Online ahead of print).

V. Popplewell MA, Andronis L, Davies HOB, Meecham L, Kelly L, Bate G, Bradbury AW. Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for Chronic Limb Threatening Ischaemia. *J Vasc Surg*. 2021 Sep 2:S0741-5214(21)01975-3 (Online ahead of print).

LIST OF PRESENTATIONS ARISING FROM THIS THESIS

I. A retrospective analysis of infra-popliteal intervention for severe limb ischaemia. Vascular Society of Great Britain and Ireland. Bournemouth, UK. 2015

II. Comparison of outcomes following infra-popliteal endovascular intervention in the BASIL-1 trial (1999-2004) with outcomes in a contemporary series (2009-2013). Society for Vascular Surgery. Washington DC, USA. 2016

III. BASIL trial: a comparison of outcomes in patients randomised to infra-popliteal vein bypass or plain balloon angioplasty. Charing Cross Symposium. London, UK. 2017

IV. BASIL trial: a comparison of outcomes in patients randomised to infra-popliteal vein bypass or plain balloon angioplasty. Controversies and Updates in Vascular Surgery. Paris, France. 2017

V. Mid-term salvage following plain balloon angioplasty for chronic limb threatening ischaemia due to infra-popliteal disease: a comparison of the BASIL trial (1999-2004) with a contemporary series (2009-2013). British Society of Endovascular Therapy. Tortworth, UK. 2017

VI. Mid-term salvage following plain balloon angioplasty for chronic limb threatening ischaemia due to infra-popliteal disease: a comparison of the BASIL trial (1999-2004)

with a contemporary series (2009-2013). European Society of Vascular Surgery. Lyon, France. 2017

VII. Emerging trials in the management of CLTI. American Heart Association Scientific Sessions. Los Angeles, USA. 2017

VIII. Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia. Vascular Society of Great Britain and Ireland. Manchester, UK. 2021 .

1 INTRODUCTION

1.1 SETTING & AIMS

Peripheral arterial disease (PAD) caused by atherosclerosis ranges in clinical severity from asymptomatic disease to intermittent claudication (IC) (pain in the leg on walking relieved by rest), to chronic limb threatening ischaemia (CLTI) which is characterised by ischaemic pain at rest (often worse at night) and/or tissue loss (ulceration, gangrene).

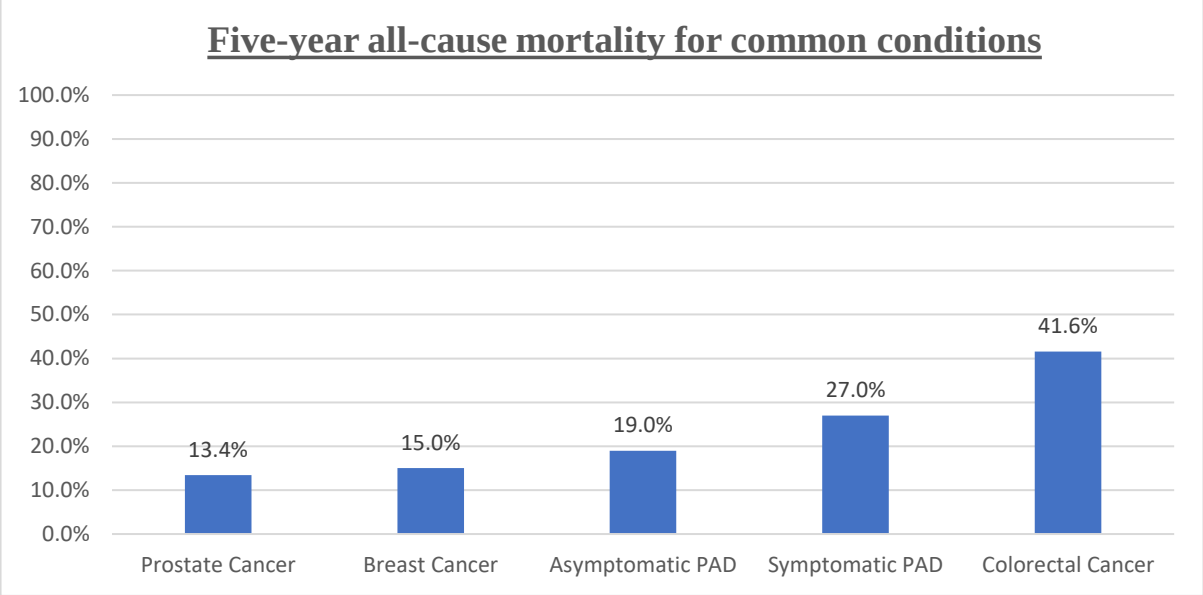
The main risk factors for CLTI are smoking, diabetes, high blood pressure (BP) and cholesterol, excessive alcohol intake, and end-stage renal disease (ESRD)[1,2]. The incidence of CLTI has been reported at around 500-1000 per million[3] and world-wide is a common cause of morbidity and mortality.

The prevalence of PAD varies by country and socio-economic status and the quality of epidemiological data is poor. PAD is estimated to have increased by 13-25% during the last decade and affects around 200 million people worldwide[3]. Once diagnosed with PAD, patients have an estimated doubling in their risk of cardiovascular related morbidity and mortality even without the presence of CLTI[4]. The number of patients living with PAD is likely to increase given the rise in diabetes, obesity and increasing tobacco use in middle to low income countries[3,5]. Compared to diseases which are equally common, awareness of PAD is low, despite survival rates being poorer than those with some common cancers[6,7] (Figure 1.1.1).

Despite this the evidence-base underpinning the management of CLTI remains poor[8,9] as is patient and public awareness[10].

The aim of the work proposed in this Thesis is to use the vehicle of the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) funded, multi-centre, UK-based: Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1 and BASIL-2)[11,12] randomised controlled trials (RCT) to explore the current management of patients with atherosclerotic PAD secondary to Infra-popliteal (IP) +/- femoro-popliteal (FP) disease at an academic vascular centre in the UK.

Figure 1.1.1 Five-year all-cause mortality for common conditions



Cancer mortality statistics taken from Cancer Research UK data (2013-2017)[6]. PAD mortality statistics taken from systematic review by Sigvant et al[7].

1.2 CHRONIC LIMB THREATENING ISCHAEMIA (CLTI)

The "Global Vascular Guidelines (GVG) on CLTI" have recently been published and aim to establish a new evidence-based framework for clinicians to operate within[13,14]. These guidelines were produced as part of a collaborative effort by the Society of Vascular Surgery (SVS), the European Society of Vascular Surgery (ESVS) and the World Federation of Vascular Societies

(WFVS). The aim of the GVG is to stimulate a paradigm shift away from a "lesion-based mentality" to provide "evidence-based revascularisation" (EBR). Definitions and terminology to describe CLTI have changed over time which has made comparison of patients in various studies a challenge due to heterogeneity. Definitions in the past with strict haemodynamic criteria for the diagnosis of "critical limb ischaemia" have excluded patients with extremely calcified vessels and those with diabetes. The term CLTI is all encompassing and includes all patients who are at risk of limb threat from wounds, advanced ischaemia, neuropathy and infection[13]. The term purposefully avoids the use of inclusive haemodynamic indices.

1.2.1 Definitions & Common Classification Systems

The first clinical classification or definition of critical limb ischaemia (CLI) was in 1952 with the publication of the Fontaine classification; which divided PAD into 4 stages (with sub-divisions)[15]. In 1986, the Rutherford classification was published and described six clinical disease stages as well objective criteria for diagnosis[16]. A revised Rutherford classification was published in 1997[17]. The Rutherford classification expanded on the four grades suggested by Fontaine by sub-stratifying claudication (mild/moderate/severe) and CLI (rest pain/minor tissue loss/major tissue loss).

In 1991, the Trans-Atlantic Intersociety Consensus (TASC) group published the following adapted from the European Consensus document on CLI[2]:

1. Persistently recurring ischaemic rest pain for more than two weeks with an ankle systolic pressure of ≤50mmHg and/or toe systolic pressure of ≤30mmHg.
2. Ulceration or gangrene of the foot or toes with an ankle systolic pressure of ≤50mmHg and/or toe systolic pressure of ≤30mmHg.

The TASC group published further guidance in 2000[18] and 2007[8]. In 2007, they proposed the following definition: "chronic ischaemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease".

The term "sub-critical limb ischaemia" (SCLI) coined by Wolfe et al, describes an intermediate stage between IC and CLI where patients have severe pain but do not quite meet the definition of CLI[19]. The advent of the term "severe limb ischaemia" (SLI) is an all-encompassing term focused on purely clinical descriptors which is described as rest pain or tissue loss secondary to PAD[20].

Although not always useful in clinical practice, definitions are required for the standardised selection and reporting of patients in clinical trials. In this Thesis the term CLTI will be used.

1.2.2 Important endpoints in CLTI

The section below details the definitions of endpoints and outcomes used throughout this Thesis to provide clarity in the chapters that follow.

Amputation Free Survival (AFS)

Composite endpoint of freedom from death from all causes and major, above the ankle amputation. AFS was the primary endpoint used in the BASIL-1 trial and is also used BASIL-2. AFS is often used as a primary endpoint throughout this Thesis.

Overall Survival (OS)

Simply defined as freedom from all-cause mortality. Often deployed as a secondary outcome in the BASIL trials collectively and in the results section of this Thesis.

Major Adverse Limb Event (MALE)

Composite outcome that corresponds to arterial intervention (surgical or endovascular) or major amputation above the ankle of the index limb studied. MALE was not frequently used over the last decade (and so not in BASIL-1), it is however reported in BASIL-3 and parts of this Thesis.

Major Adverse Cardiac Event (MACE)

MACE occurs when an individual is reported as experiencing death from all causes, myocardial infarction, cerebrovascular accident or cardiac revascularisation (percutaneous or open). MACE is often reported in the coronary literature and is mentioned sporadically throughout this Thesis.

Freedom from re-intervention (FF-R)

Describes freedom from both open surgical and endovascular procedures following the primary intervention.

Limb Salvage (LS)

Describes freedom from above the ankle amputation. This includes below the knee, through the knee and above the knee amputations.

Quality of Life (QoL) instruments

Vascular Quality of Life Questionnaire (VascuQoL)

The VascuQoL questionnaire[21] features 25 questions relating to different facets of symptomatic PAD (activity, symptoms, pain, social and emotional). A summative mean score out of 7 is expressed as an 'overall; score, 7 representing the best disease specific QoL and 1 representing the worst.

EuroQol 5 dimensions 5 levels (EQ 5D 5L) index

Generic QoL instrument (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/) which is used to describe health in 5 dimensions including: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question has 5 levels of health status (no problems, slight problems, moderate problems, severe problems and extreme problems). Following completion an index is derived from 0 (death) to 1 (perfect health).

Visual analogue scale (VAS)

The visual analogue scale is a generic QoL measure which also is used in conjunction with the EQ 5D 5L instrument. Patients are asked to grade their health on a scale of zero to 100, where zero represents no perceived health, and 100 represents perfect health.

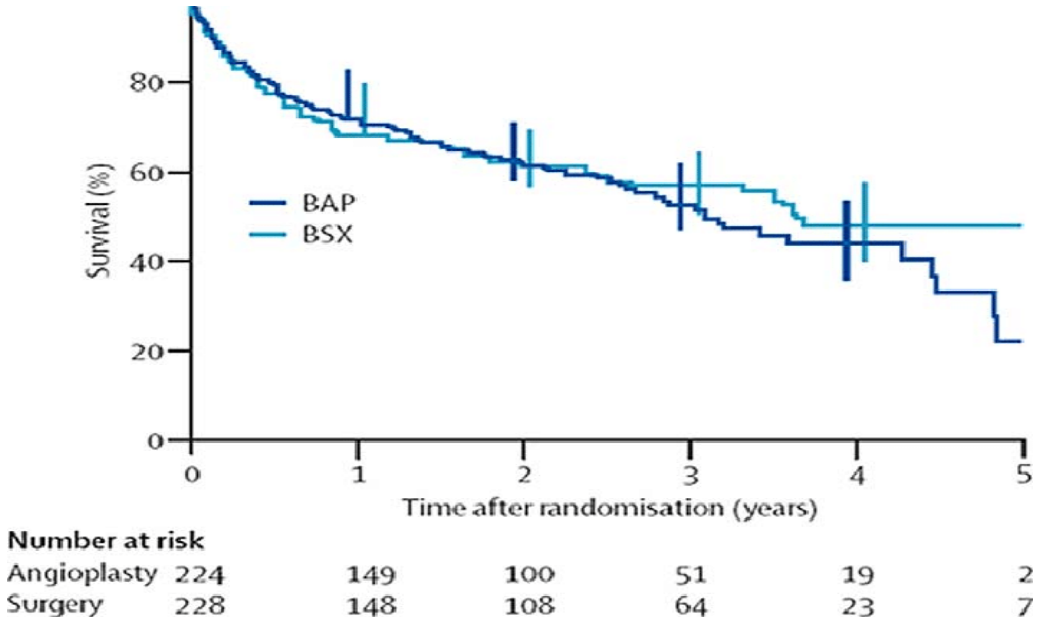
1.3 EVIDENCE AND GUIDELINES IN CLTI

1.3.1 The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) - 1 Trial

The UK NIHR HTA funded BASIL-1 trial remains the only published randomised controlled trial (RCT) to compare BS and plain balloon angioplasty (PBA) for the treatment of CLTI due to infra-inguinal disease (http://www.nets.nihr.ac.uk/projects/hta/960501)[9].

BASIL-1 randomised 452 patients to bypass surgery (75% with vein conduit) or PBA (six patients also had bare metal stents (BMS) all in the superficial femoral artery (SFA). Although around 25% of patients underwent revascularisation for IP +/- FP disease, the trial was not powered to demonstrate treatment effects in this subgroup. In patients who survived more than 2 years after randomisation, BS was associated with better outcomes in terms of AFS (Figure 1.3.1) and overall survival (OS). In patients who did not survive for 2 years, there was no significant difference in AFS or OS.

Figure 1.3.1 Amputation Free Survival in the BASIL-1 trial



Abbreviations: BAP, Balloon angioplasty; BSX, Bypass Surgery. Figure taken from the BASIL Trial[11].

The BASIL-1 trial has been criticised by some regarding generalisability as only 29% of screened subjects in the BASIL audit were deemed suitable for entry into the trial, 68% of which were randomised. This trend is seen in current clinical trials in patients with CLTI, as patients present with heterogeneous patterns of disease which can make standardisation difficult.

Although the National Institute of Health and Care Excellence (NICE) multi-disciplinary expert guideline committee (CG147) mainly based its recommendations on CLTI revascularisation strategies on data from the BASIL-1 trial, it recognised that BASIL-1 was primarily a trial of FP interventions.

As such, the committee's view was that there remained considerable uncertainty as to whether CLI patients requiring an IP revascularisation, and who could have distal vein bypass (VB), should receive VB or best endovascular therapy (BET) as their first revascularisation procedure. For this reason, NICE recommended a further RCT in this area and NIHR HTA subsequently funded the BASIL-2 trial which compares the clinical and cost-effectiveness of VB and BET for the treatment of CLTI due to IP disease (http://www.nets.nihr.ac.uk/projects/hta/123545)[12].

1.3.2 Summary of NICE Clinical Guideline 147

In 2012, NICE released guidelines for UK healthcare professionals regarding the diagnosis and management of PAD[22]. Clinical Guideline 147 (CG147) detailed a framework for best practice based on current evidence for the whole spectrum of PAD, focusing on diagnosis, investigation and management of patients. Specific guidance for patients with CLTI is displayed in Table 1.3.1.

Due to a lack of evidence the guidance is rather vague, in that no specific treatment recommendations are made. The process of formulating NICE guidance involves the review of the highest level of evidence. Regarding CLTI this is somewhat problematic given that BASIL-1, to date, is the only published, publicly funded RCT to compare treatment modalities.

Despite these recommendations, many still ignore NICE recommendations and increasingly, an "endovascular first" revascularisation strategy is employed. This is not uncommon, as other parts of the guideline (regarding intervention in patients with IC) are also largely ignored by healthcare providers and commissioners despite strong evidence to suggest to the contrary[23].

Table 1.3.1 NICE Clinical Guideline 147 – Recommendations in CLTI

NICE CG147 Recommendations in CLTI
Offer angioplasty or bypass surgery for CLTI in those who require revascularisation, considering comorbidity, pattern of disease, availability of vein and patient choice.
Do not offer primary stent placement
Use bare metal stents where stenting is required
Use autologous vein whenever possible when performing infra-inguinal bypass surgery
Do not offer major amputation to patients unless all revascularisation options have been explored

Adapted from NICE clinical guideline CG147[22]

1.3.3 The Bypass versus Angioplasty in Severe Ischaemia of the Leg – 2 Trial

Many may argue that endovascular outcomes from BASIL-1[9] are outdated given the advances in catheters, wires, access and treatment devices over the last decade, and whilst that may be true in chronological terms, there are still no publicly funded, randomised trials published that compare BET and vein bypass (VB) in the IP segment. Unfortunately, the evidence base underpinning the management of CLTI due to IP disease remains extremely limited[24–28]. Present data indicate that it is far from clear that patients with CLTI who require IP revascularisation and who are suitable for VB should have BET as their primary procedure.

The Bypass versus Angioplasty of the Leg -2 (BASIL-2) trial is the first, publicly funded RCT to compare the clinical and cost-effectiveness of a BET first versus a VB first strategy for patients with CLTI primarily due to IP disease[12]. The trial is funded by the NIHR HTA within the UK and has now completed randomising patients in the UK, Sweden and Denmark. BASIL-2 initially aimed to randomise 600 patients (in equal groups) to either strategy, aiming to detect a difference of one third (Hazard Ratio 0.66) in AFS at 3-years with 90% power. However, the challenges in recruitment have led to patients in the trial being followed up for longer than

anticipated. This coupled with a higher than predicted endpoint rate (AFS) has led to a decrease in target recruitment to around 380 patients, whilst maintaining equivalent statistical power.

BASIL-2 collects detailed information at baseline regarding; patient history, pulse status, haemodynamics (Ankle Brachial Pressure Index/Toe Brachial Pressure Index), imaging, detailed wound assessment (using The Society for Vascular Surgery - Wound Ischaemia foot Infection system[29] and the Perfusion Extent Depth Infection Score[30]) and information regarding health related of quality of life (HRQoL) using generic (Visual Analogue Scale, European Quality of Life 5 level score, Short-Form 12, Hospital Anxiety and Depression scale) and disease specific tools (Vascular Quality of Life).

Following randomisation to either BET or VB, patients are followed up at pre-specified time points out to 36 months, collecting information regarding the status of the patient and the trial leg as well as HRQoL. The specifics of the BASIL-2 Consolidated Standards of Reporting Trials (CONSORT) diagram are detailed below (Figure 1.3.2)[12].

Although there seems to be broad agreement that BASIL-2 is addressing an important research question, recruitment was difficult. This is mainly because, despite a lack of supporting evidence, a significant body of vascular surgeons and interventional radiologists appear to believe that a BET-first revascularisation strategy is clearly preferable for most, even all, patients with CLTI due to IP disease, and that VB should be reserved for those who cannot have or fail BET.

1.3.4 The Balloon versus Stenting in Severe Ischaemia of the Leg – 3 Trial

The Balloon versus Stenting in Severe Ischaemia of the Leg – 3 (BASIL-3) is currently randomising CLTI patients with FP +/- IP PAD in equal proportions to three separate

endovascular interventions; PBA with optional BMS, Drug Coated Balloon (DCB) with BMS if required or primary Drug Eluting Stenting (DES).

The trial is powered at 90% to detect a reduction of 40% (HR 0.60) in AFS at 3.3 years when PBA +/- BMS is compared to the two other treatment arms individually.

BASIL-3 will collect similar variables at baseline to those stated above as for BASIL-2. The primary outcome is AFS, secondary outcomes of OS, MALE, in-hospital and 30-day mortality and morbidity, MACE, relief of ischaemic rest pain as measured by VAS, cross over and reintervention rates, healing of tissue loss as assessed by WIfI and PEDIS, haemodynamic changes following revascularisation and HRQoL (generic and disease specific).

BASIL-3 was initially recruiting well, reaching approximately 50% of the original target 861 patients until the publication of controversial data regarding the use of paclitaxel based interventional devices[31]. Katsanos et al, in 2018 published a systematic review and meta-analysis of 4,663 patients from 28 RCTs who underwent endovascular treatment (paclitaxel-based stents and balloons versus PBA) for mainly IC secondary to FP disease. The group reported an increased all-cause mortality for those treated with paclitaxel-based devices (relative risk (RR) 1.93, number needed to harm 14). Following a pause of 9 months and rigorous review by the scientific community, BASIL-3 reopened to recruitment, due to significant doubt regarding generalisability of these data to patients with CLTI as 90% of patients in the analysis presented with IC. At the time of writing the trial is near completion and is due to report in late 2022.

Figure 1.3.2 The BASIL-2 CONSORT Diagram

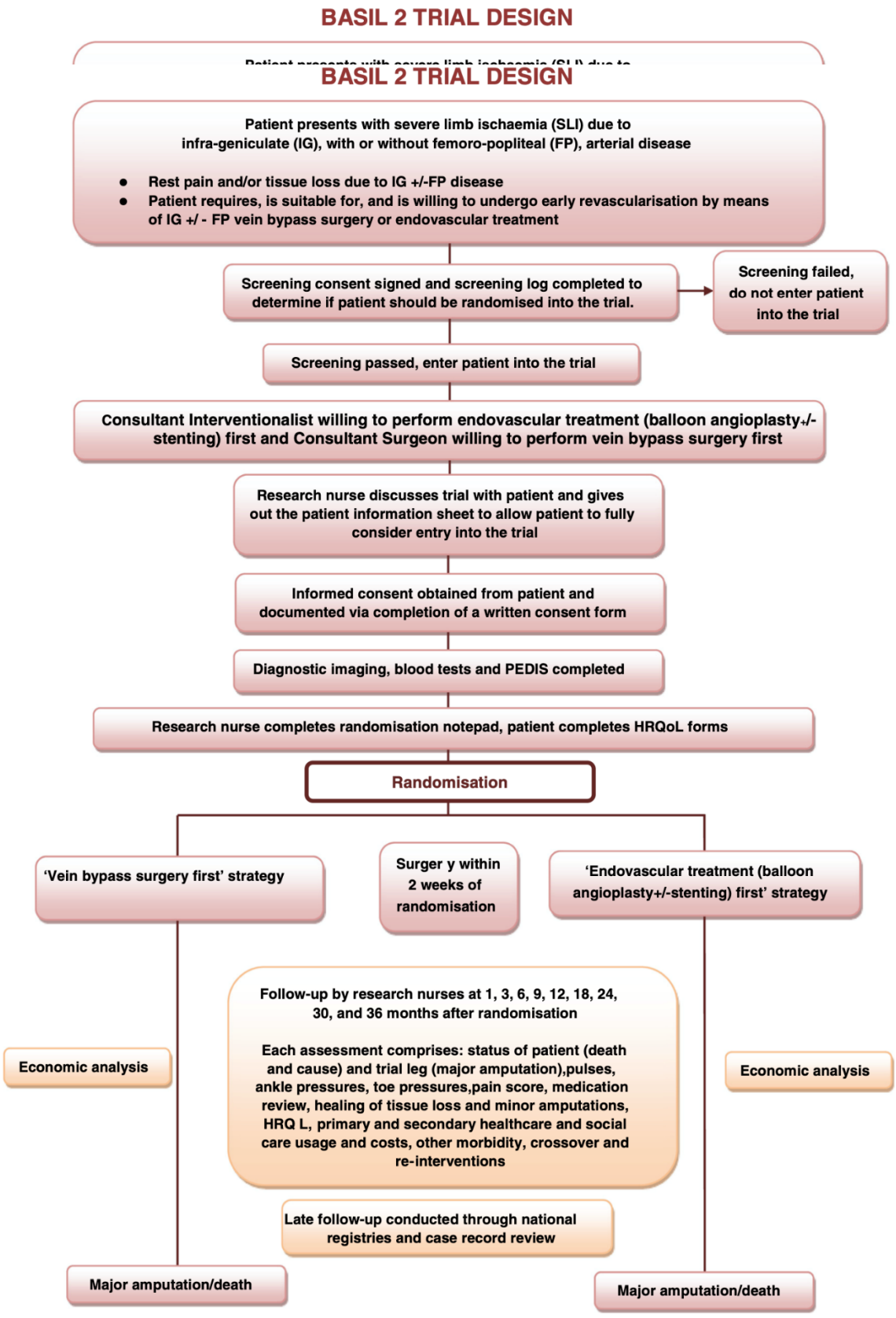


Figure taken from the BASIL-2 trial protocol[12].

1.3.5 SWEDEPAD 1 &2

The Swedish Drug-elution Trial in Peripheral Arterial Disease (SWEDEPAD) which opened in 2014 also aimed to recruit patients into separate studies exploring the efficacy of drug-eluting technology versus control (PBA). SWEDEPAD-1 randomises patients with CLTI whilst SWEDEPAD-2 concerns those with IC. The primary outcome of SWEDEPAD-1 is AFS, with secondary outcomes of OS, time to target lesion revascularisation, patency, improvement in clinical symptoms and HRQoL. In similar fashion to BASIL-3, SWEDEPAD closed to recruitment following the publication of the Katsanos meta-analysis but has since reopened. The authors have since published an unplanned interim analysis in December 2020 in response, demonstrating no differences in all-cause mortality between patients undergoing angioplasty either with drug coated or uncoated device at 1-4 years[32]. SWEDEPAD is due to complete recruitment in October 2022 (https://clinicaltrials.gov/ct2/show/NCT02051088). Both BASIL-3 and SWEDEPAD will provide important data regarding the use of drug eluting technology.

1.3.6 The Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischaemia (BEST-CLI) Trial

The Best Endovascular versus Best Surgical Therapy in patients with Critical Limb Ischaemia (BEST-CLI) trial, is the first US RCT to compare such treatment strategies. BEST-CLI aims to examine similar outcomes to those in BASIL-2, in all patients with infra-inguinal disease (not just IP disease) such as treatment efficacy, functional outcomes, HRQoL and costs[33]. This multicenter, prospective superiority trial was aiming to randomise 2100 patients with CLTI over 140 centers in the US and is funded by the National Heart, Lung and Blood Institute. Unlike BASIL-2, where patients who do not have a suitable autologous venous conduit are excluded, BEST-CLI comprises two separate patient cohorts; those with and without great

saphenous vein conduit. The primary outcome of the trial is freedom from major adverse limb event (FF-MALE).

Similarly, to BASIL-2 and 3, recruitment into BEST-CLI had been slow and difficult despite adequate funding and many enrolled sites. The trial has now surpassed its 50-month study target duration has ended active recruitment in February 2020, reaching 1,843 of the originally planned target of 2,100 patients. Unlike BASIL-2, the BEST-CLI trial was powered to detect a 25% reduction in AFS to 80% power. It is unclear the impact that the reduced sample size will have on statistical power as, like in BASIL-2 the trial is endpoint driven. The BEST-CLI, BASIL-2 and BASIL-3 trialist have agreed to perform an individual patient data meta-analysis which will further increase the volume of level 1 evidence.

1.4 GLOBAL VASCULAR GUIDELINES ON CLTI

The SVS, ESVS and WFVS have jointly published the Global Vascular Guidelines on CLTI [13,14]. The aims of the Global Vascular Guidelines (GVG) are to improve outcomes in patients with CLTI by the following[34];

1. Promoting paradigms and tools as a framework for evidence based revascularisation
2. Making specific practice recommendations based on GRADE* levels of evidence
3. Identifying gaps in the evidence and suggesting areas and methods for future research

**GRADE – Grading of Recommendations, Assessment, Development and Evaluations*

The GVG proposes the use of a number of paradigms and tools to improve structured decision making in the management of CLTI in an attempt to achieve evidence-based revascularisation.

1.4.1 Initial patient assessment

The assessment of a patient with suspected CLTI should always begin with a thorough history, examination and screening for known risk factors related to PAD. Limb threat is then assessed firstly by the measurement of non-invasive haemodynamics. This process as suggested by the recent GVG was followed throughout prospective data collection for this Thesis. Some detail regarding the methods and the evidence underpinning them is detailed below.

1.4.2 Non-invasive haemodynamic testing

In all patients with suspected CLTI the GVG recommend the measurement of ankle systolic pressures (AP) as well as the ankle brachial pressure index (ABPI)[13]. This non-invasive measure provides haemodynamic information regarding perfusion of the limb. In the presence of calcification, particularly in those with diabetes and chronic kidney disease such measurements can be falsely elevated. Such measurements should always be correlated with Doppler arterial waveforms to assess the quality of signal (monophasic, biphasic or triphasic) as well as absolute systolic pressures. In cases of severe calcification, the GVG suggest the use of toe brachial pressure indices (TBPI) and waveforms as the digital vessels seem to be spared from medial calcinosis. These modalities are reported throughout this Thesis.

1.4.3 The SVS Threatened Limb Classification System (WIfI)

In 2013, the SVS produced the Wound Ischaemia Foot infection (WIfI) classification to predict the estimated risk of major lower limb amputation (MLLA) at 1-year in patients with CLTI. The WIfI system uses a paradigm similar to the “Tumour, nodes, metastases” classification used in the staging of malignant disease. The user stages the wound in terms of size, the presence of ischaemia denoted by non-invasive haemodynamics and the presence of foot infection. Due to its relative complexity, WIfI has been used mostly in the context of research. WIfI has been validated externally, supporting the use of the tool to predict amputation and

mortality[35]. The BASIL-2, BASIL-3 and BEST-CLI trials are all collecting WIfI at baseline which may lead to further validation and development of the tool in the future. WIfI was also used prospectively in data collected at baseline for this Thesis.

1.4.4 Perfusion Extent Depth Infection and Sensation classification system (PEDIS)

Although not routinely recommended for use in the GVG, the PEDIS system is used in the BASIL-2 trial. The tool was developed for use primarily in patients with diabetic foot ulceration (DFU). Users are asked to grade the five variables all of which are associated with poorer prognosis in terms of limb threat. PEDIS has been validated in a retrospective cohort of over 300 patients[30]. PEDIS is used at baseline and during follow up visits for those patients in BASIL-2 with tissue loss as well as in the prospective data collection of patients for this Thesis.

Figure 1.4.1 details the pathway each patient presenting with suspected CLTI should follow when assessed by a vascular clinician[13,14]. The group recommend that all patients with abnormal ABPI should undergo TBPI which is not currently part of routine clinical practice the UK. This recommendation is based on evidence from the 'Cohorte des Patients ARTeriopathes' (COPART) registry, where investigators reported a strong association with an absolute toe pressure of 30mmHg or less with major amputation. In the same cohort ABPI alone 'failed to identify' 42% of patients with CLTI[36]. Following these assessments, if considered appropriate, imaging is used to help plan revascularisation. The GVG recommend that in the first instance this should be non-invasive[13].

1.4.5 Non-invasive imaging

Duplex Ultrasonography (DUS)

DUS is the recommended first line investigation in patients with suspected CLTI based on level 2B evidence[37]. DUS is relatively cheap, avoids the use of ionising radiation and is a mobile

investigation that provides detailed information regarding the anatomical location and extent of PAD[38–40].

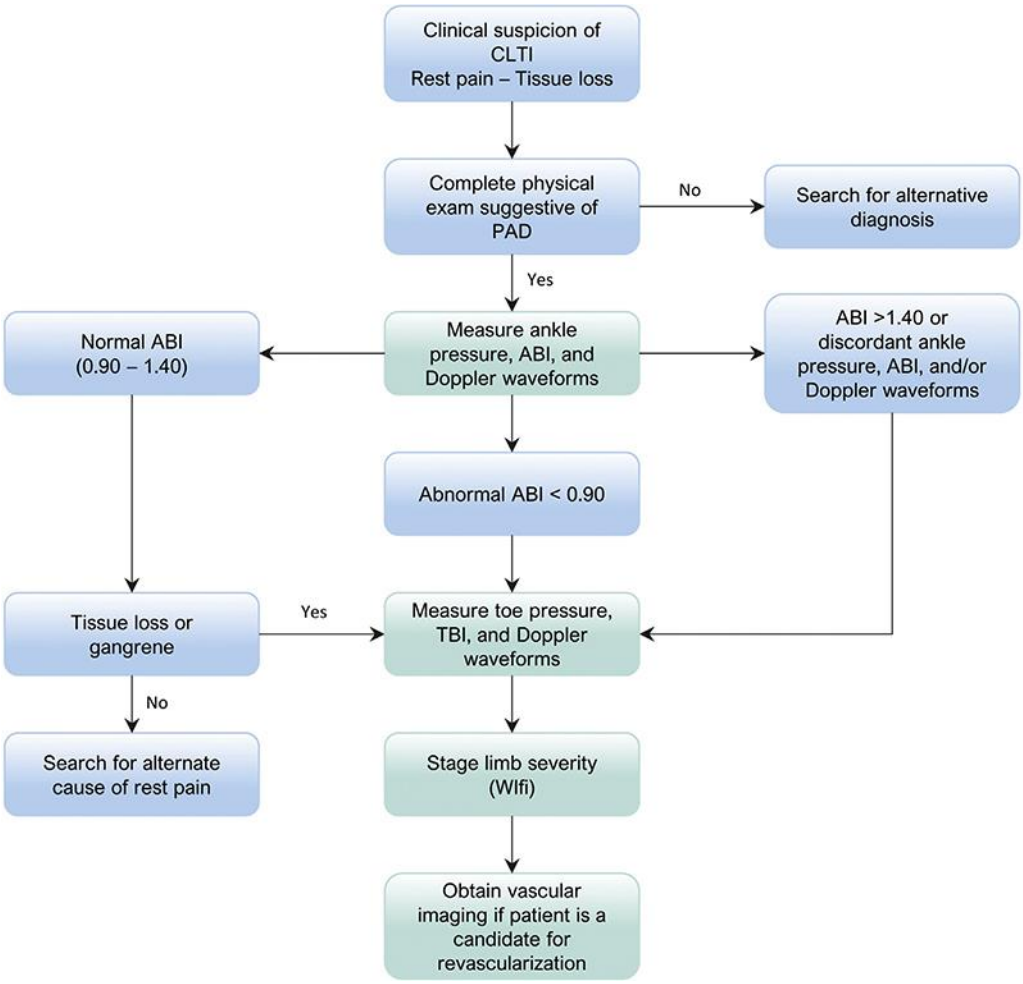
Computed Tomography Angiogram (CTA)

In recent times the quality and accuracy of CTA has significantly improved with the use of three-dimensional reconstruction and multi-planar imaging[41,42]. When compared to digital subtraction angiography (DSA), others have found CTA to be highly sensitive and specific in the aortoiliac (AI) and FP segments but less so in the IP segment[43].

The usefulness of CTA in the IP segment is largely limited by the "blooming effect" of calcified arteries, prominent in diabetic and renal patients. CTA is readily available in most vascular institutions but carries the risk of contrast induced nephropathy[44], particularly in those with pre-existing renal disease[45]. CTA exposes individuals to relatively high doses of ionising radiation which must be considered; particularly when multiple imaging sequences are required in the future[46].

When performed by experienced and specialist operators, MRA can provide images of similar accuracy and quality to DSA without the use of ionising radiation or iodine-based contrast agents[47,48]. MRA is more sensitive and specific than CTA and DUS[49]. To some, the claustrophobic nature of MRA is unacceptable and others who have implanted medical devices are contraindicated from entering the scanner. Gadolinium contrast enhancement is preferred, despite the small risks of nephrogenic systemic fibrosis.

Figure 1.4.1 Flow diagram for the investigation of patients presenting with CLTI



Magnetic Resonance Imaging Angiography (MRA). Figure taken from the Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischaemia[14].

1.4.6 Invasive imaging

Digital Subtraction Angiography (DSA)

DSA is still considered by many as the gold standard when imaging for infrainguinal disease, particularly in the IP segment[50]. Many argue that during imaging users can proceed directly to endovascular intervention if prior consent has been gained. DSA is widely available and has a relatively low complication rate. DSA can be performed with minimal iodine-based contrast,

however where this is contraindicated, carbon dioxide can be used as a contrast agent with varying image quality in the IP segment[13].

1.4.7 Patient risk, Limb threat, and ANatomic severity of disease (PLAN)

Following collation of the metrics detailed above, the GVG asks clinicians to consider revascularisation based on the PLAn principle which is detailed below.

PLAN comprises;

- **P**atient risk estimation;
    - Candidacy for limb salvage
    - Peri-procedural risk
    - Life expectancy
- **L**imb threat severity using the SVS Wound Ischaemia foot Infection (WIfI) staging system[29]
- **An**atomic pattern of disease using the **Gl**obal **A**natomic **S**taging **S**ystem (GLASS)

1.4.8 The Global Anatomic Staging System (GLASS)

The GLASS starts with defining the "target artery pathway" (TAP) that will be used during the proposed endovascular revascularisation to establish in line flow to the foot and depends on the availability and review of high-quality imaging. The target IP artery is usually the least diseased but may be angiosome specific. The term "angiosome" refers to the target artery that supplies blood to an area of tissue loss[51]. There is considerable debate as to whether this direct form of revascularisation is superior to indirect revascularisation given that up to 50% of wounds are limited to the digits which receive supply both from the anterior and posterior tibial arteries[52]. The evidence base supporting angiosomal based revascularisation is severely confounded and limited[53,54].

Following TAP selection, the user grades (1-4) the burden of disease in the FP and IP segments to derive an overall GLASS stage (from I to III, Table 1.4.1 & Table 1.4.2). The GLASS stages were designed pragmatically to predict immediate endovascular treatment failure and the likelihood of "limb-based patency" (LBP) at 12-months[34].

LBP is defined as "maintenance of inline flow throughout the TAP from the SFA origin to the malleoli"[13]. LBP is considered to be lost when there is anatomical failure (critical stenosis, occlusion or re-intervention) or haemodynamic failure (significant drop in ABPI or TBPI, stenosis of >50% without resolution of symptoms) within the TAP.

GLASS has been validated using data from BASIL-1 by our research team demonstrating good correlation with endovascular outcomes (AFS, OS, LS, FF-MALE) but no correlation with outcomes following bypass surgery[55].

Table 1.4.1 Global Anatomic Staging System (GLASS) Grades

FP segment
0 – Mild or no significant (<50%) disease
1 – Total length SFA disease <1/3rd (<10cm); may include focal chronic total occlusion (CTO) (<5cm) as long as not flush occlusion; popliteal artery with mild or no significant disease
2 – Total length SFA disease 1/3rd to 2/3rd (10-20cm) may include CTO totalling <1/3rd (10cm) but not flush occlusion; focal popliteal artery stenosis <2cm not involving the trifurcation.
3 – Total length SFA disease >2/3rd (>20cm) length; may include any flush occlusion <20cm or non-flush CTO 10-20cm long; short popliteal stenosis 2-5cm, not involving the trifurcation
4 – Total length SFA occlusion >20cm; popliteal disease >5cm or extending into the trifurcation; any popliteal CTO
IP segment
0 – Mild or no significant (<50%) disease
1 – Focal stenosis <3cm not including the TP trunk
2 – Total length of target artery disease <1/3rd (<10cm); single focal CTO <3cm (not including target artery origin or TP trunk)
3 – Total length of target artery disease 1/3rd to 2/3rd (10-20cm); CTO 3-10cm (may include target artery origin, but not TP trunk
4 – Total length of target artery disease 2/3rd in length; CTO >1/3rd (>10cm) of length (may include target artery origin); any CTO of the TP trunk

*Abbreviations: SFA, superficial femoral artery; CTO, chronic total occlusion; TP, tibioperoneal. *Of note: Severe calcification in the selected segment increases the grade by +1. TP trunk disease is only taken into consideration if the IP TAP is the peroneal or posterior tibial. Adapted from the 'Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischaemia'*[13].

Table 1.4.2 Global Anatomic Staging System (GLASS) stages based on Femoro-popliteal and Infra-popliteal grades.

INFRA-INGUINAL GLASS STAGE						
FP Grade	**4**	III	III	III	III	III
	3	II	II	II	III	III
	2	I	II	II	II	III
	1	I	I	II	II	III
	0	n/a	I	I	II	III
IP Grade		**0**	**1**	**2**	**3**	**4**

Abbreviations: FP, femoropopliteal; IP, infrapopliteal. Table adapted from the 'Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischaemia'[13].

GLASS Stage 1 - average complexity, expected technical failure of <10% and >70% LBP at 12-months.

GLASS Stage II - intermediate complexity, expected technical failure of <20% and 50-70% LBP at 12-months.

GLASS Stage III - high complexity, estimated technical failure of >20% and <50% LBP at 12-months.

1.5 MANAGEMENT OF CLTI AND EVIDENCE BASED REVASCULARISATION IN THE IP SEGMENT

1.5.1 Conservative/Medical management

All patients with CLTI should be offered best medical therapy (BMT) and have their risk factors addressed. This involves aggressive control of diabetes and hypertension, smoking cessation and the prescription of an antiplatelet agent (clopidogrel) and moderate/high intensity statin[13]. In BASIL-1 the prescribed rates of BMT were low, with around one third of patients taking lipid lowering therapy and two-thirds taking antiplatelets at the time of referral[11]. Despite many

studies including the Swedish National Vascular Registry, reporting that statins can reduce the risk of a secondary cardiovascular event in patients undergoing revascularisation for CLTI, the prescription of BMT, like in BASIL-1 is still generally poor (around 60%)[56].

Best Medical Therapy

In the UK, NICE recommend an antiplatelet agent (Clopidogrel 75 milligrams once daily) and lipid lowering therapy[22] (A high-intensity dose statin agent such as 80 milligrams of Atorvastatin daily as first line) as widely used in patients with coronary artery disease (CAD). Research into the use of direct oral anticoagulants, dual antiplatelets and combinations of the two continue. Ongoing genomic testing is investigating targeted alleles expressed in some patients who cannot metabolise antiplatelet therapies; which may have screening implications in the future. There are wider issues however around compliance, adherence and patient and public education; even in large prospective clinical trials the uptake of "BMT" is poor at around 70%[9,57,58]. Outside of clinical trials, the most recent UK National Vascular Registry (NVR) report (2020)[59], estimates prescription rates of 83.8% in elective, open revascularisation procedures and only 76.1% in non-elective equivalents. From personal experience, this is largely due to patient statin intolerance and 'reluctance to take stigma' from statin 'bad press' in the mid noughties. This is disappointing given the extent of high-quality evidence available to clinicians regarding statin use in secondary prevention of cardiovascular disease. More is required on a public health frontier to educate patients and families regarding the positives of such treatment.

Direct Oral Anti-Coagulants (DOACs)

In 2019 the publication of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial reported that adjunctive, low dose rivaroxaban (2.5 milligrams

twice daily) therapy combined with aspirin (100mg) reduced MALE by 43% at the expense of increase rates of bleeding[60]. In 2020, this combination, was recommended for use in the UK by NICE in patients with CLTI who are considered at high risk of further ischaemic events (age over 65, atherosclerosis in at least two vascular territories or two of the following risk factors; active smokers, diabetics, eGFR 15-60ml/min, heart failure, previous non-lacunar ischaemic stroke)[61].

The Rivaroxaban in Endovascular or Surgical Limb Revascularisation for PAD (VOYAGER PAD) trial published its outcomes in May 2021[62]. The study reported that in those receiving low dose rivaroxaban (2.5mg twice daily) plus aspirin (100mg once daily) had a reduction in primary efficacy outcome (incidence of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke, or death from cardiovascular causes) when compared to those receiving aspirin (100mg once daily) plus placebo (HR 0.85, 95%CI: 0.76-0.96; p=.009). However, there were variable reports on major bleeding rates depending on the classification system used to determine if a major bleeding event had occurred (Thrombolysis in Myocardial Infarction (TIMI) – no significant difference in bleeding; International Society on Thrombosis and Haemostasis (ISTH) – significantly higher bleeding rates with rivaroxaban + aspirin compared to aspirin alone, HR 1.42, 95%CI: 1.10 – 1.84; p=.007). Despite current evidence and proactiveness of industry to use rivaroxaban, many clinicians remain cautious using such combination given the increased bleeding risk. Most PAD patients exhibit significant frailty and intracranial or gastrointestinal bleeding in this cohort is often deadly. Even though approved for use in some hospital trusts DOACs are still ‘non-formulary’ for the indications in the COMPASS and VOYAGER PAD trials and therefore there is some resistance or difficulty in obtaining hospital prescription which may also be a barrier to its use. Uptake

and acceptability of rivaroxaban in primary care following hospital prescription is currently unknown given the likely increased costs associated.

Anti-platelet therapy

The Platelet Inhibition and patient Outcomes (PLATO) trial demonstrated a reduction in secondary cardiac events when ticagrelor was given with aspirin as dual antiplatelet therapy in patients with acute coronary syndrome[63]. When ticagrelor was given as monotherapy and outcomes were compared in patients with symptomatic PAD there were no reductions in cardiovascular morbidity when compared with clopidogrel alone[64]. Evidence from the US Vascular Quality Initiative (VQI) demonstrated survival benefit in patients undergoing lower limb revascularisation when dual anti-platelet therapy (aspirin plus any P2Y12 inhibitor) was used[65]. Such drugs (e.g. clopidogrel, prasugrel and ticagrelor) act by blocking the P2Y12 receptors that are responsible for adenosine diphosphate stimulated activation of the glycoprotein IIb/IIIa receptor. These actions increase platelet degranulation and thromboxane production which in turn prolongs platelet aggregation[66]. The use of clopidogrel is now fairly commonplace in patients with CLTI, however the use of dual antiplatelets is more controversial with varying practices up and down the UK. In similar fashion to rivaroxaban, there remains concerns regarding increased bleeding risk. Anecdotally, dual therapy is often used when an intervention has been performed that is at high risk of treatment failure or when the last 'roll of the dice' has been used in limb salvage. There are no specific protocols in use currently, both dual therapy and rivaroxaban use seems to be at the interventionalist's or surgeon's discretion at the time of writing.

Lipid modification

The Heart Protection Study examined outcomes in 6,748 patients with PAD who were randomly allocated to simvastatin 40mg once daily or a placebo. The study reported a 16% relative risk reduction in peripheral vascular events[67]. The Reduction of Atherothrombosis for Continued Health (REACH) registry examined 5,861 patients and reported a 14% relative risk reduction in a composite endpoint of worsening IC, critical limb ischaemia (the term CLTI was not in use at the time), peripheral revascularisation and amputation at 4 years[68].

Guidelines in the US, UK and the rest of Europe recommend the use of high intensity statin to reduce secondary cardiovascular events[13,22,69]. One study reported that patients with CLTI had reduced mortality and improved freedom from MALE when lipid therapy guidelines where followed in patients undergoing arterial revascularisation[70].

1.5.2 Untreated CLTI

Patients who are unsuitable for revascularisation are managed by primary amputation or analgesia, palliation and dressing care. It is estimated that half of all patients with CLTI do not undergo revascularisation[22]. A systematic review in 2016 by Abu Dabrh et al, reported all-cause mortality and major amputation at 12 months at 22% in those with untreated CLTI. The group also commented on trends toward improving outcomes in more recent times, owning to improved medical therapy[71]. Little is known regarding health status or HRQoL in this patient subgroup as compared to those undergoing revascularisation[72]. It is considered best practice to explore all options with high quality imaging prior to offering primary amputation or conservative treatment unless this is clinically indicated[13]. This Thesis aims to explore this patient group in more detail, given the lack of high quality, prospective data in the literature. It is often assumed that patients with CLTI are discharged home to a palliative setting, but it is

unknown how long these patients actually survive, what their quality of life is like and the care that they receive in this time following discharge from hospital.

1.5.3 Plain Balloon Angioplasty

Endovascular therapy is frequently used as first line intervention for CLTI[73], with variable outcomes following PBA[74]. A systematic review and meta-analysis by Mustapha et al from 2016 reported a primary technical success of 91.1%, a primary patency of 63.1% at 12-months with a repeat intervention rate of 18.2% in the same follow-up period. Major, above the ankle amputation (14.9%) and all-cause mortality (15.1%) were relatively poor at 12-months[75]. The authors did however comment that the data were heterogenous and, therefore, comparison between studies was difficult. The primary technical success of endovascular IP intervention (including stenting) has been quoted between 56-100%, with a pooled estimate of 89.0% +/- 2.2%[24]. Although BASIL-1 reported outcomes on patients undergoing FP+/- IP PBA +/- bare metal stenting (BMS), the subgroup of patients with IP disease have not yet been examined. These patients are examined in some detail in this Thesis.

At present, PBA in the UK is still considered as the first line of treatment for patients with CLTI. Some clinicians remain sceptical about the use of endovascular treatment in the IP segment due to perceived increased risk of technical failure and poorer outcomes than vein bypass. Following the heated debate surrounding drug technology many have resorted to PBA alone with or without bailout bare metal stenting as the sole endovascular treatment option. There are individuals and units at some centres who have and use a variety of endovascular devices to treat CLTI secondary to IP disease including; drug technology, atherectomy, shockwave therapy and re-entry devices but many of these techniques or devices lack strong publicly funded evidence to support their use or demonstrate cost-effectiveness above and beyond PBA.

1.5.4 Drug Eluting Technology

Due to the nature of endovascular treatment of the infrainguinal vessels post-treatment plain balloon angioplasty sites are prone to restenosis through the process 'neo-intimal hyperplasia'[76]. To combat this some have investigated the use of angioplasty balloons and stents that utilise anti-proliferative drugs such as paclitaxel with initially promising angiographic results[77].

In February 2020 the Katsanos group published data regarding the use of paclitaxel coated balloons in patients with CLTI secondary to IP disease[78]. This systematic review and meta-analysis reviewed 1,420 patients from 8 RCTs. The group reported worsening AFS in those undergoing paclitaxel-based intervention compared to those receiving control (PBA, RR 1.52). The causation of this remains unclear; although the group have suggested non-target embolisation of paclitaxel as a factor, but this is purely speculation.

Some point to the fact that some of the data used in this analysis was from the IN.PACT DEEP trial (Amphirion paclitaxel coated balloon versus standard percutaneous transluminal angioplasty for IP revascularization of CLI trial) which was stopped early, amid safety concerns due to a higher MLLA rate at 12 months (8.8% vs 3.6%) in the DCB arm[79]. This device has now been withdrawn from the market and is no longer in use. What is clear is that two separate large meta-analyses have reported associated increasing mortality with the use of paclitaxel-based devices, and this must not be discounted.

In June 2019, the Medicines and Healthcare Regulatory Agency (MHRA) published guidance regarding the use of such devices. The expert advisory group (EAG) enlisted to perform the review commented that the Katsanos methodology was sound and that the use of paclitaxel-based devices in patients with IC should cease. Due to considerable doubt regarding mortality

effects in patients with CLTI the EAG recommended continued use of such devices in clinical trial settings only (e.g. BASIL-3)[80]. In the US, the Food and Drug Administration (FDA) have taken a slightly different stance and encourage extended monitoring, reporting and careful balancing of risks in patients selected for endovascular treatment with paclitaxel-based devices[81].

Contrary to this, in the IP segment some data exist that supports the use of drug eluting stents (DES) in short to medium length lesions resulting in; improved patency, less restenosis and better reduction in Rutherford grade in comparison with PBA[82]. At the time of writing drug eluting stents are not routinely kept as consignment stock in most UK vascular centres and are not used routinely in clinical practice. Potential reasons for this include increased costs, unfamiliarity with device usage and the lack of long-term data pertaining to longer lesions.

In the UK, there is still (at the time of writing) some reluctance to use drug coated devices when treating CLTI secondary to IP disease. The BASIL-3 trial struggled to complete recruitment following a pause in the wake of the Katsanos meta-analysis and users seem to reserve drug eluting treatment for recurrent or residual stenoses during secondary revascularisations as opposed to a primary treatment. Data from BASIL-3, BEST-CLI and SWEDEPAD 1 & 2 are sorely needed to investigate the mortality risk in greater detail.

1.5.5 Bypass Surgery

In previous decades, surgical bypass was considered the “gold standard” treatment for patients with CLTI due to FP +/- IP disease. The outcomes of such bypass grafts are well documented in the literature. IP vein grafts have 5-year patency rates of 50-70%, with a limb salvage rate more than 80% in most cohorts[8]. Post-operative (30-day) mortality is around 3%, however morbidity is generally higher (around 20%) with increased lengths of stay in hospital after the

index revascularisation procedure. The use of continued follow-up with vein graft surveillance programmes is used widely due to the occurrence of significant stenosis in 20-40% of patients within 2-years following surgery [83].

Autologous vein is the preferred conduit as opposed to prosthetic material due to significantly poorer outcomes demonstrated in many studies, including BASIL-1[9]. Vein bypass is probably the choice of revascularisation method for most clinicians when good venous conduit is present, patients are fit enough to withstand open surgery and there is good inflow and outflow prospects on detailed imaging. Unfortunately, many patients fall outside of these categories for one or more reasons, which has directed clinicians towards other, less invasive, less resource intensive methods of revascularisation. Modern evidence on which to base practice in 2021 is lacking and it seems that patients are less fit, older and have more comorbidity than those examined in earlier randomised trials.

1.5.6 Evidence-Based Revascularisation

Systematic review and meta-analyses of nine RCT's comparing open and endovascular revascularisation for all patients with infrainguinal CLTI reported similar mortality (Odds Ratio [OR], 0.72; 95% confidence interval [CI], 0.44-1.16) and amputation (OR, 1.2; 95% CI, 0.87-1.65) rates following treatment[25]. Patients undergoing VB however had significantly improved primary patency (OR, 2.50; 95% CI, 1.25-4.99) and assisted primary patency (OR, 3.39; 95% CI, 1.53-7.51) when compared to endovascular treatment. The authors of this review commented that overall the quality of evidence was low.

Based on the current best available evidence the GVG recommend that all average risk patients with available venous conduit should be revascularised according to the preferred strategy. A "preferred strategy" is based on patient wishes, the availability of resources (theatre space,

equipment) and skill set of the attending vascular and endovascular practitioners. The PLAN framework (Figure 1.5.1) sets out a suggested strategy for managing patients with CLTI. An average risk patient is defined as those with an expected peri-procedural mortality of <5% and a 2-year life expectancy of >50%[13,14].

Those considered to be high risk (mortality >5%, 2-year life expectancy <50%) should be offered endovascular treatment. There remains a lack of consensus regarding the treatment of intermediate risk patients with ranging clinical and anatomical complexity and further evidence in such patients is clearly required[13,14]. Those without venous conduit are recommended to be offered endovascular treatment if suitable owing to poor outcomes from prosthetic and biological grafts[84].

Methods used in the GVG are still in their relative infancy and are not currently adopted into mainstream clinical practice. For example, as previously mentioned, GLASS has been externally validated using retrospective data but in its current form is too cumbersome and too time consuming to be used in 'real world' practice outside the setting of research. More work is needed to refine the PLAN methodology (including the application of GLASS) before it is successfully integrated into routine practice. It does however, represent a step in the right direction regarding thought processes and use of EBR that is clearly required in patients with CLTI.

Figure 1.5.1 The PLAN Framework for managing patients with CLTI

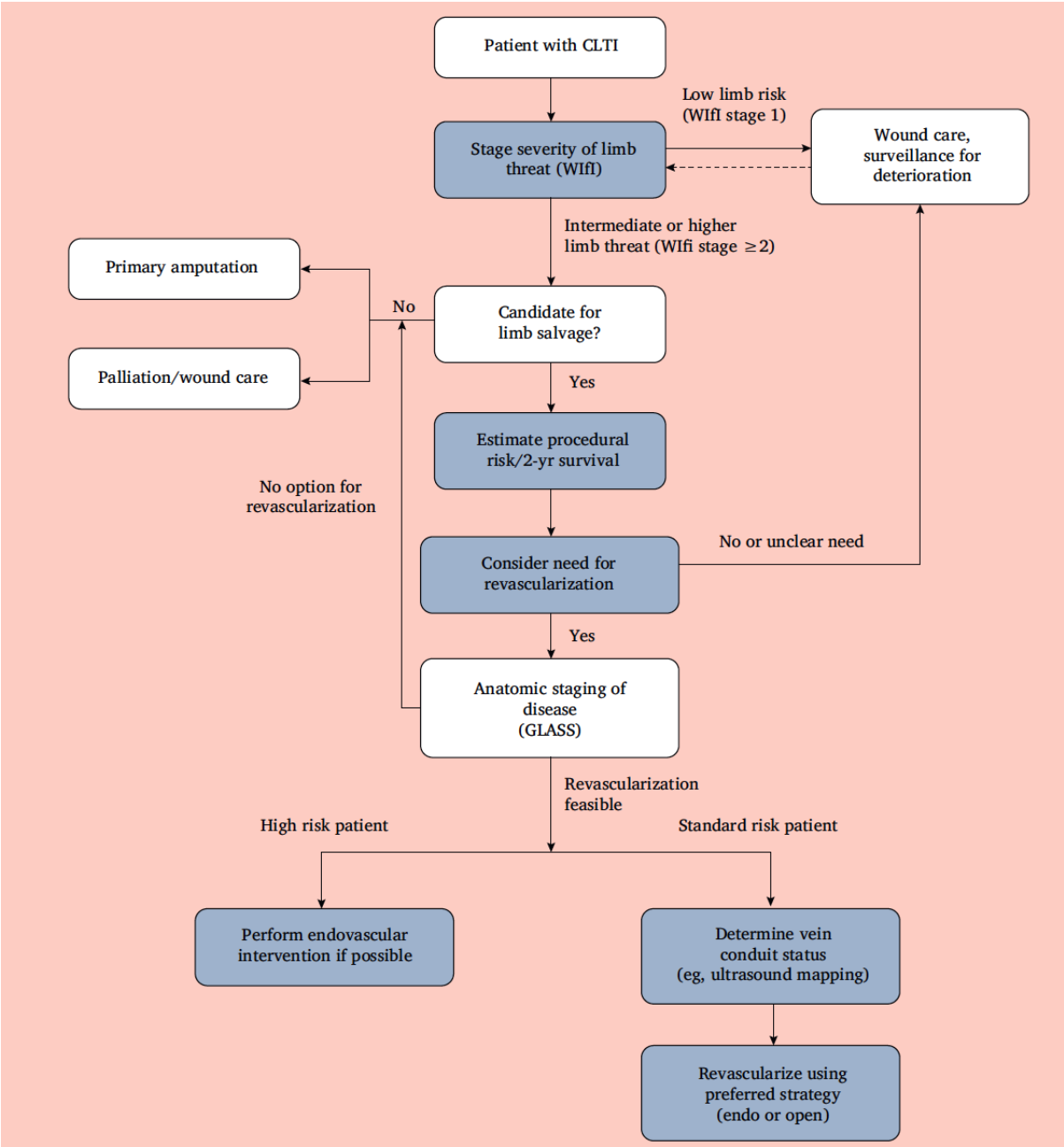


Figure taken from the 'Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischaemia'[13].

1.5.7 Major Lower Limb Amputation (MLLA)

MLLA aims to provide relief of pain, removal of grossly infected tissues, promotes primary healing of to allow the preservation mobility and or independence if possible[13]. The GVG advise this may be necessary in circumstances where revascularisation has not been attempted due to[13];

- Non-re-constructible disease
- Tissue loss involving the weight bearing portion of the foot
- Non-functional limb due to ischaemic contracture.
- Palliation – for those in severe pain or discomfort
- Or when multiple procedures are required which are likely to have limited success in the presence of frailty/co-morbidity.

If revascularisation has failed and the patient falls into any of the above categories, then secondary amputation should be considered. Peri-operative morality is estimated at 4-22% for patients undergoing MLLA[85].

In 2010, the Vascular Society of Great Britain and Ireland (VSGBI) produced a quality improvement framework (QIF) aimed at reducing mortality in such patients to less than 10% within 30-days from surgery. Currently, 30-day mortality reported by the National Vascular Registry (NVR) from MLLA was documented at 11.6% for those undergoing above knee amputation (AKA) and 6.1% in those undergoing below knee amputation (BKA)[86]. Similar results have been reported in the US from the National Surgical Quality Improvement programme (12.7% AKA, 6.5% BKA)[87].

1.5.8 Costing

Little is known or reported regarding the cost effectiveness of revascularisation strategies. To date, the only published randomised data from publicly funded sources with regard to health economics in patients undergoing intervention for CLTI emanates from the BASIL-1 trial[88]. The group reported increased costs for those undergoing VB initially ($34,378 vs. $25,808 PBA). Over the follow up period these costs equilibrated ($45,322 for VB vs $39,801 for PBA). Given the lack of data in the literature, this Thesis will also examine the impact of revascularisation on costs in a modern cohort of patients undergoing intervention for CLTI secondary to IP disease.

RCTs in the long-term should remain the gold standard for determining the clinical and cost effectiveness of treatment strategies in CLTI[89]. Such studies should ideally report outcomes in terms of cost per quality of adjusted life year (QALY) so that cost effectiveness can be measured against current willingness to pay thresholds (currently £20,000 in the UK)[90].

1.6 SUMMARY

Whilst small observational studies are numerous in the IP literature there is still paucity in high quality evidence to determine a "first" treatment strategy. The use of new endovascular technology was on the increase despite a lack of significant evidence, however, the impact of the studies published by Katsanos in 2018 and 2020 remain to be seen[31,78]. The clinical cost and effectiveness of revascularisation strategies can only be determined by a combination of RCTs and good, well maintained prospective cohort studies and registries to provide clinicians with high quality, long-term outcome data. Current economic and political challenges should not deter VS and IR from offering patients important clinical studies such as the BASIL-2 and BEST-CLI trials[12,33]

Given the review above there are clearly many areas in were evidence is lacking regarding the management of CLTI due to IP disease. To answer some of the research questions that could be generated from this would require large multicenter RCTs with significant support and funding.

The aim of this Thesis is to explore current areas of the management of IP CLTI where data is most lacking to inform future RCTs and to confirm the ongoing need for the BASIL-2 trial. Firstly, data from the BASIL-1 trial will be examined pertaining to those patients undergoing either bypass surgery or PBA for CLTI secondary to IP+/-FP disease. As previously stated, endovascular outcomes in this group are thought by some to be outdated and irrelevant to more modern practice. With this in mind the aim is compare the IP subgroup of patients from BASIL-1 with a cohort of patients from a single academic vascular unit in East Birmingham, UK between 2009 and 2013. To stimulate debate and anticipate what findings BASIL-2 may demonstrate this endovascular cohort of patients from East Birmingham will be compared with similar patients undergoing bypass surgery.

Currently in the UK, prospective data collection relies on sources from publicly maintained registries such as the National Vascular Registry[59] and Hospital Episode Statistics (HES) data[91]. The NVR relies the quality of end-user (clinician) input and is notoriously inaccurate and under-reported particularly in patients with CLTI[59]. Data obtained from HES relies on clinical coding acquisition from hospital discharge summaries details which is also notoriously inaccurate. Due to these factors, at our institution we prospectively collected data on all patients attending with CLTI to describe and compare; outcomes in those that undergo revascularisation, outcomes in those who do not or undergo MLLA and hospital resource usage. Collectively this will be referred to as the BASIL Prospective Cohort Study (BASIL-PCS).

This will not only apply to patients undergoing revascularisation, but the entire cohort of patients who present with IP CLTI, this will provide generalisability and a context for comparison between those undergoing intervention as compared to those managed conservatively.

1.7 ACKNOWEDGEMENT OF COLLABORATIVE CONTRIBUTIONS

This section describes the contribution of other authors for work contained in this Thesis. The work presented in sections 2.1, 2.2, 2.3 and 2.4 are representations of published work from a variety of vascular scientific journals. I (Matthew A Popplewell) was the first author on all four papers.

Section 2.1 co-authors;

Mr Huw Davies – Assisted with design and critical appraisal of final manuscript.

Miss Joyti Narayanswami – Assisted with data collection and data sorting of original trial data.

Dr Mary Renton – Assisted with data collection and data sorting of original trial data.

Dr Alex Sharp – Assisted with data collection and data sorting of original trial data.

SN Gareth Bate – Lead research nurse on the original BASIL trial. Provided data access and assistance with data extraction.

Mrs Smitaa Patel – Provided statistical advice and support.

Professor Jon Deeks – Provided statistical advice and support.

Professor Andrew Bradbury – Senior author, responsible for overall review of process.

Section 2.2 co-authors;

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Dr Mary Renton - Assisted with data collection and data sorting of original trial data.

SN Gareth Bate - Lead research nurse on the original BASIL trial. Provided data access and assistance with data extraction.

Mrs Smitaa Patel - Provided statistical advice and support.

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SN Gareth Bate – Assisted with data extraction from original BASIL trial.

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Section 2.4 co-authors;

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SN Gareth Bate – Assisted with data extraction from original BASIL trial.

SN Lisa Kelly – Assisted with data entry

Mrs Tracy Ellis – Assisted with data entry

Professor Andrew Bradbury - Senior author, responsible for overall review of process.

Section 2.5 co-authors;

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Mr Huw Davies - Assisted with study design and critical appraisal of final manuscript.

Mr Lewis Meecham – Assisted in data collection in times of absence.

SN Lisa Kelly – provided database support.

SN Gareth Bate - Assisted in data collection in times of absence.

Professor Andrew Bradbury - Senior author, responsible for overall review of process.

2 RESULTS

OVERVIEW

Sections 2.1 to 2.3 are retrospective analyses of clinical data both from the BASIL-1 trial and the Heart of England Foundation Trust – University Hospitals Birmingham (HEFT UHB). Section 2.1 is a comparative subgroup analysis of those patients randomised to IP plain balloon angioplasty or vein bypass during the BASIL-1 trial. Section 2.2 aims to compare the outcomes of those patients randomised to IP plain balloon angioplasty in the BASIL-1 trial with a more modern cohort of similar patients taken from HEFT UHB between 2009 to 2013. Section 2.3 is an analysis of clinical outcomes in patients from HEFT UHB that underwent either PBA or vein bypass prior to the start of BASIL-2 and the BASIL-PCS (2009-2013).

Section 2.4 is a summary of the findings from the BASIL-PCS were 259 patients with CLTI were studied in detail following emergency admission to HEFT UHB between 2014 and 2016. The primary focus of this study was regarding those with infrainguinal disease as well as detailed screening for BASIL-2.

Finally, section 2.5 aims to estimate the costs of caring for patients with CLTI secondary to IP disease during their index BASIL-PCS admission and in the 12-months following discharge from hospital.

2.1 A COMPARISON OF OUTCOMES IN PATIENTS WITH INFRA-POPLITEAL DISEASE RANDOMISED TO VEIN BYPASS OR PLAIN BALLOON ANGIOPLASTY IN THE BYPASS VERSUS ANGIOPLASTY IN SEVERE ISCHAEMIA OF THE LEG TRIAL

The BASIL-1 trial initially reported outcomes in 2005. In the cohort of 452 patients, around 25% had revascularisation for primarily IP disease. The trial was not powered to show treatment differences in AFS in this IP subgroup, however, it gives a historical control to base any future comparisons. Patients in BASIL-1 had been considered suitable for both treatment modalities prior to randomisation, although, venous conduit was not available in all as prosthetic bypass at the time was still considered a reasonable treatment option. This data is therefore unique as it compares patients suitable for both treatments without selection bias.

2.1.1 Abstract

Objective:

The aim was to compare outcomes in a subgroup of patients with infrapopliteal (IP) disease randomised to infrapopliteal vein bypass (VB) or plain balloon angioplasty (PBA) in the original BASIL-1 trial.

Methods:

A comparison of outcomes from patients randomised to VB or PBA undergoing revascularisation for chronic limb threatening ischaemia (CLTI) because of IP disease with or without femoropopliteal disease. Data were extracted from case report forms from the BASIL-1 trial. The primary outcome was amputation free survival (AFS); secondary outcomes included overall survival (OS), 30-day mortality and morbidity, freedom from arterial re-intervention,

immediate technical success, repeat and crossover interventions, length of hospital stay, and quality of revascularisation.

Results:

A total of 104 patients were identified in the BASIL-1 study with IP disease, 56 randomised to IP VB, and 48 to IP PBA. Groups were similar at baseline except for more chronic kidney disease and non-steroidal anti-inflammatory drug use in the VB group, and more previous surgical arterial intervention and antihypertensive use in the PBA group. There were no statistically significant differences in AFS or OS; however, clinically important trends were apparent in favour of a VB first strategy. Patients allocated to VB demonstrated significantly quicker relief of rest pain when compared with PBA ($p = .005$), but no significant differences in improved tissue healing. Median length of index hospital admission was significantly greater in the VB than in the PBA group (18 vs. 10 days, $p < .0001$) but there was no difference between the two groups in median total hospital stay between randomisation and the primary endpoint (VB 43.5 vs. PBA 42 days).

Conclusions:

Further randomised trials, like BASIL-2 and BEST-CLI, are required to determine whether patients with CLTI who require IP revascularisation and who are suitable for VB should have bypass or endovascular intervention as their primary revascularisation procedure.

2.1.2 Introduction

The UK National Institute of Heath Research (NIHR) Health Technology Assessment (HTA) funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial remains the only published randomised controlled trial (RCT) to compare bypass surgery with angioplasty

for the treatment of chronic limb threatening ischaemia (CLTI) comprising rest pain, tissue loss, or both (http://www.nets.nihr.ac.uk/projects/ hta/960501)[9].

The BASIL trial randomised 452 patients with CLTI, defined as rest pain, tissue loss, or both because of atherosclerotic peripheral arterial disease, to bypass surgery (75% with vein) or plain balloon angioplasty (PBA) (6 patients also had bare metal stents). Around 25% of patients underwent revascularisation for CLTI as a result of infrapopliteal (IP) disease with or without femoropopliteal (FP) disease; however, the trial was not powered to demonstrate effects in this subgroup.

In patients who survived more than 2 years after randomisation, bypass was associated with a better outcome in terms of amputation free survival (AFS) and overall survival (OS). By contrast, in patients who did not survive for 2 years, there was no significant clinical difference between the two treatment arms in terms of major amputation or mortality. In August 2012, the UK National Institute for Health and Care Excellence (NICE) published its national Clinical Guidelines (CG 147) on Peripheral Arterial Disease (https:// www.nice.org.uk/guidance/cg147)[22]. Although the multidisciplinary expert guideline committee mainly based its recommendations on CLTI revascularisation strategies on data from the BASIL-1 trial, it recognised that BASIL-1 was primarily a trial of FP interventions. As such, the committee's view was that there remained considerable uncertainty as to whether CLTI patients requiring an IP revascularisation, and who could have distal vein bypass (VB), should receive VB or best endovascular therapy (BET) as their first revascularisation procedure. For this reason, NICE recommended a further RCT in this area and NIHR HTA subsequently funded the BASIL-2 trial, which compares the clinical and cost effectiveness of VB and BET for the treatment of CLTI due to IP disease (http://www.nets.nihr.ac.uk/projects/hta/123545)[12].

Although there seems to be broad agreement that this is an important question, recruitment to BASIL-2 has been difficult. This is mainly because, despite a lack of supporting evidence, a significant body of vascular surgeons and interventional radiologists believe that a BET first revascularisation strategy is clearly preferable for most, even all, patients with CLTI due to IP disease, and that VB should be reserved for those who cannot have or fail BET.

To generate discussion around the question posed by BASIL-2, clinical outcomes have been compared in a subset of patients randomised to IP VB or PBA within the original BASIL-1 trial.

2.1.3 Methods

During the trial, 452 patients with CLTI as a result of infrainguinal disease were randomised between August 1999 and June 2004 from 27 different UK hospitals to a VB first or PBA first strategy. The original BASIL-1 case report forms (CRFs) were interrogated for those patients randomised to IP VB or PBA. Patients in this subgroup had either PBA with or without bare metal stent or VB with the distal target vessel below the popliteal artery (including the tibioperoneal trunk and beyond). Patients with grafts using prosthetic material were excluded (including composite sequential), as this no longer reflects current clinical practice (Figure 2.1.1).

The primary outcome was AFS; secondary outcomes included OS, 30-day mortality and morbidity, freedom from arterial re-intervention, immediate technical success rates, repeat and crossover interventions, length of hospital stay. Quality of life as measured by VascuQoL[21] and EuroQoL 5D plus visual analogue scale (VAS) (https://euroqol.org) was reported at baseline, 3-months, 6-months and 12-months. Although Short-Form-36 (SF-36) raw scores were available in the data we did not have a valid license for interpretation, calculation and comparison. For this reason, the SF-36 scores were excluded from the quality of life analysis.

The quality of revascularisation was also assessed in terms of improvement in ankle brachial pressure index (ABPI), number of days to cessation of rest pain, and healing of ischaemic wounds and/or 'minor' amputations. Time to event outcomes were recorded over 5 years of follow-up and are presented using Kaplan-Meier plots. For each Kaplan Meier curve estimate once the number at risk reaches less than 20% of the total cohort results should be interpreted with caution as survival estimates are likely to become less reliable. Differences between groups are estimated as hazard ratios (HR) computed from the log-rank statistic. Quality of life data was analysed in accordance with the BASIL trial methodology which is described elsewhere[88]. The authors present 95% confidence intervals for each HR to describe the range of treatment effects compatible with the observed data. Differences in other outcomes are assessed using t-tests, chi-square tests and Wilcoxon rank sum tests according to data type and distributional shape. All analyses were performed with an intention-to-treat analysis with data censored on 1st July 2007. Analyses were undertaken in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Figure 2.1.1 BASIL-1 Trial Schema

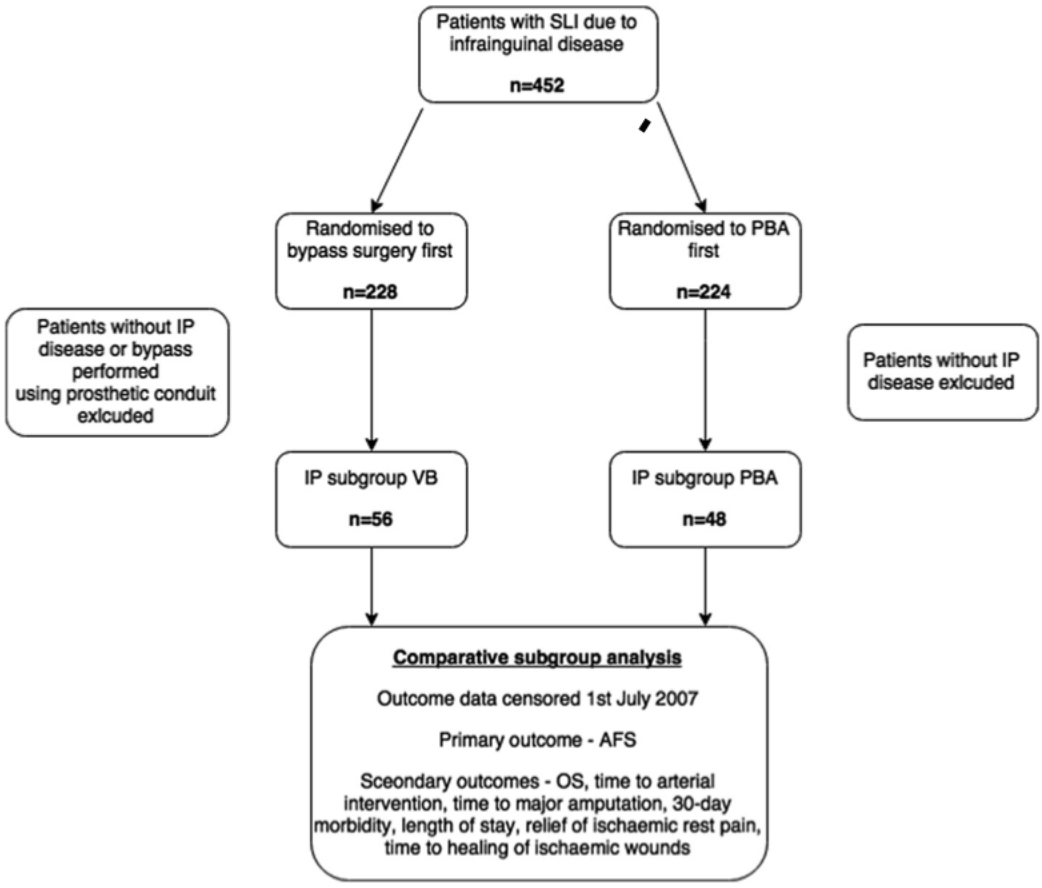


Figure adapted from the 'Bypass Versus Angioplasty in Severe Ischaemia of the Leg Trial'[11]

2.1.4 Results

The 56 patients randomised to IP VB and the 48 to IP PBA were generally similar at baseline except in the VB group twice as many patients had chronic kidney disease (34% VB vs. 15% PBA) and twice as many were current smokers (25% vs. 11%); they also a had higher usage of non-steroidal anti-inflammatory drugs (23% vs. 6%). In the PBA group twice as many patients had a history of previous myocardial infarction (14% VB vs. 29% PBA) and more patients had a history of hypertension on current antihypertensive treatment (61% VB vs. 79% PBA). Previous vascular intervention was more common in the PBA group. In this group, five patients had undergone previous suprainguinal PBA, three patients had previous infrainguinal PBA, one

patient had previous infrainguinal surgery, one patient had both previous infrainguinal surgery and infrainguinal PBA, two patients had previous suprainguinal surgery, and one patient had undergone previous minor amputation surgery. Conversely in the VB group two patients had undergone previous suprainguinal PBA, one patient had previous infrainguinal PBA, one patient had previous infrainguinal surgery, one patient had previous suprainguinal PBA with stenting and concurrent infrainguinal PBA, and one patient had previous PBA in an unrecorded anatomical segment. Baseline comparisons are presented in Table 2.1.1.

Procedural details, describing anatomical variation and target vessel lesions are reported in Tables 2.1.2 and 2.1.3. Only single vessel recanalisation was attempted in most patients undergoing PBA (85%), with 15% of patients undergoing two vessel recanalisation attempts and no patients undergoing three tibial vessel recanalisation.

Primary technical success (during the BASIL-1 trial technical success was documented by the responsible surgeon or interventionalist at the time of procedure, the criteria for this was left to the discretion of the investigator) was higher for VB (86%) than for PBA (73%) (RR for technical failure 0.53, 95% CI 0.24-1.16, p .11). In four patients randomised to VB, surgery was discontinued due to a lack of an appropriate IP target vessel; another four patients suffered graft failure within 24 h.

Three patients had attempted graft thrombo-embolectomy; one graft was salvaged as a result of this, whereas two patients underwent delayed major lower limb amputation. In the PBA group, it proved impossible to cross and/or dilate the IP lesion in 10 (21%) patients; in two patients, there was distal embolisation/vessel rupture that halted the procedure; and one procedure was abandoned due to pain.

Table 2.1.1 Baseline characteristics of the BASIL-1 infra-popliteal subgroup.

	Vein Bypass (n = 56)	PBA (n = 48)	p value
Age (years) (mean, SD)	74.0 (11.3)	77.2 (7.3)	.09
Male sex	41 (73%)	32 (67%)	.5
Comorbidities			
Chronic kidney disease	19 (34%)	7 (15%)	.007
Stroke / TIA	12 (21%)	8 (17%)	.5
Myocardial Infarction	8 (14%)	14 (29%)	.06
Angina	11 (20%)	10 (21%)	.9
Dialysis	2 (4%)	0 (-)	.2
Diabetes (DM)	24 (43%)	23 (48%)	.6
Insulin dependent DM	10 (42%)	8 (35%)	.6
Smoking Status			
Current	14 (25%)	5 (11%)	.1
Ex	29 (52%)	27 (56%)	
Never	13 (23%)	16 (33%)	
Clinical Presentation			
Tissue loss	46 (82%)	41 (85%)	.7
Medical therapy			
Aspirin	38 (68%)	25 (52%)	.1
Clopidogrel	4 (7%)	3 (6%)	.9
Antihypertensive	34 (61%)	38 (79%)	.04
Statin therapy	22 (39%)	12 (25%)	.1
Warfarin	4 (7%)	5 (10%)	.6
Paracetamol	36 (64%)	29 (60%)	.7
Opiates	31 (55%)	28 (58%)	.8
NSAIDs	13 (23%)	3 (6%)	.02
Gabapentin	2 (4%)	1 (2%)	.7
Amitriptyline	5 (9%)	2 (4%)	.3
Previous Intervention			
Endovascular	5 (9%)	7 (15%)	.4
Surgical	1 (2%)	6 (13%)	.03

Table 2.1.2 Vein bypass procedural details for the BASIL-1 infra-popliteal subgroup.

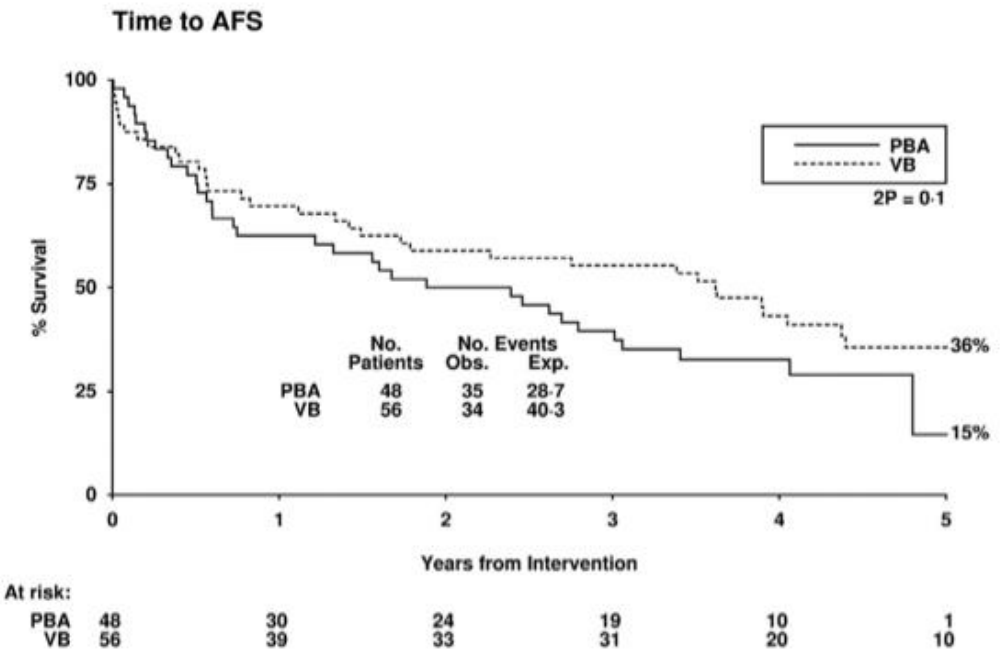
n=56		**Number**
Conduit	Reversed vein	23 (41%)
	Non-reversed vein	28 (50%)
	Leg vein	51 (91%)
	Arm vein	1 (2%)
	No bypass performed as distal target not patent	4 (7%)
Proximal anastomosis	Common femoral artery	24 (43%)
	Superficial femoral artery	18 (32%)
	Profunda femoris artery	1 (2%)
	Above knee popliteal artery	5 (9%)
	Below knee popliteal artery	5 (9%)
Distal anastomosis	Posterior tibial artery 1/3	3 (5%)
	Posterior tibial artery 2/3	4 (7%)
	Posterior tibial artery 3/3	10 (18%)
	Peroneal artery 1/3	5 (9%)
	Peroneal artery 2/3	5 (9%)
	Peroneal artery 3/3	4 (7%)
	Anterior tibial artery 1/3	6 (11%)
	Anterior tibial artery 2/3	5 (9%)
	Anterior tibial artery 3/3	6 (11%)
	Dorsalis pedis	2 (4%)
Technical failures	Graft completed but failed <24h	4 (7%)
	Abandoned, no outflow vessel	4 (7%)
	Total technical failure	8/56 (14%)

Table 2.1.3 Plain Balloon Angioplasty details BASIL-1 infra-popliteal subgroup.

n=48		**Number**
Arteries Treated	Superficial femoral	29 (60%)
	Above knee popliteal	29 (60%)
	Below knee popliteal	28 (58%)
	Tibio-peroneal trunk	4 (8%)
	Posterior tibial	9 (19%)
	Peroneal	25 (52%)
	Anterior tibial	19 (40%)
	Dorsalis pedis	1 (2%)
Attempted number of tibial vessel recanalisations	1 vessel	41 (85%)
	2 vessels	7 (15%)
	3 vessels	0 (-%)
Type of disease treated	Occlusive	23 (48%)
	Stenotic	12 (25%)
	Combination	13 (27%)
PBA and stent use	PBA only	47 (98%)
	PBA + bail out BMS	1 (2%)
Technical failure	Inability to cross lesion	6 (12%)
	Recoil (failed angioplasty)	5 (10%)
	Embolism	1 (2%)
	Abandoned at patient request	1 (2%)
	Total technical failure	13/48 (27%)

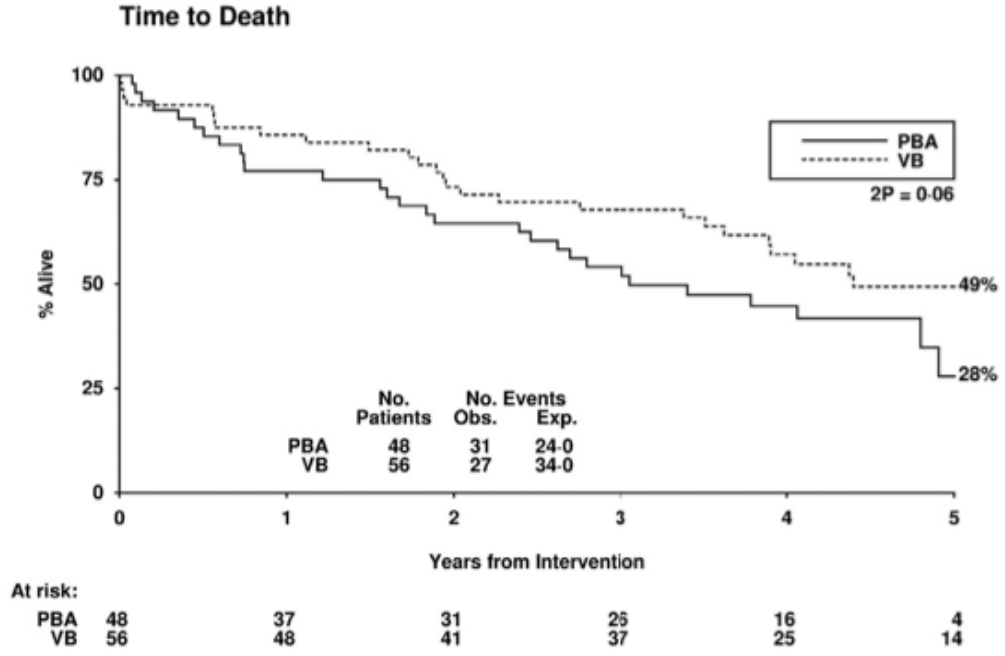
From these 13 patients, four went on to have VB, four had no further intervention, three had a repeat attempt at PBA, one had a below knee amputation (BKA), and one patient underwent common femoral endarterectomy and profundaplasty. AFS was 32% lower in the PBA group than VB group (HR 0.68, 95% CI 0.42-1.10, p .1) (Figure 2.1.2) and OS 40% lower in the PBA group (HR 0.60, 95% CI 0.36-1.02, p .06) (Figure 2.1.3).

Figure 2.1.2 Amputation Free Survival in the BASIL-1 infrapopliteal subgroup analysis.



Amputation Free Survival. HR 0.68, 95% CI 0.42-1.10, p= .1.

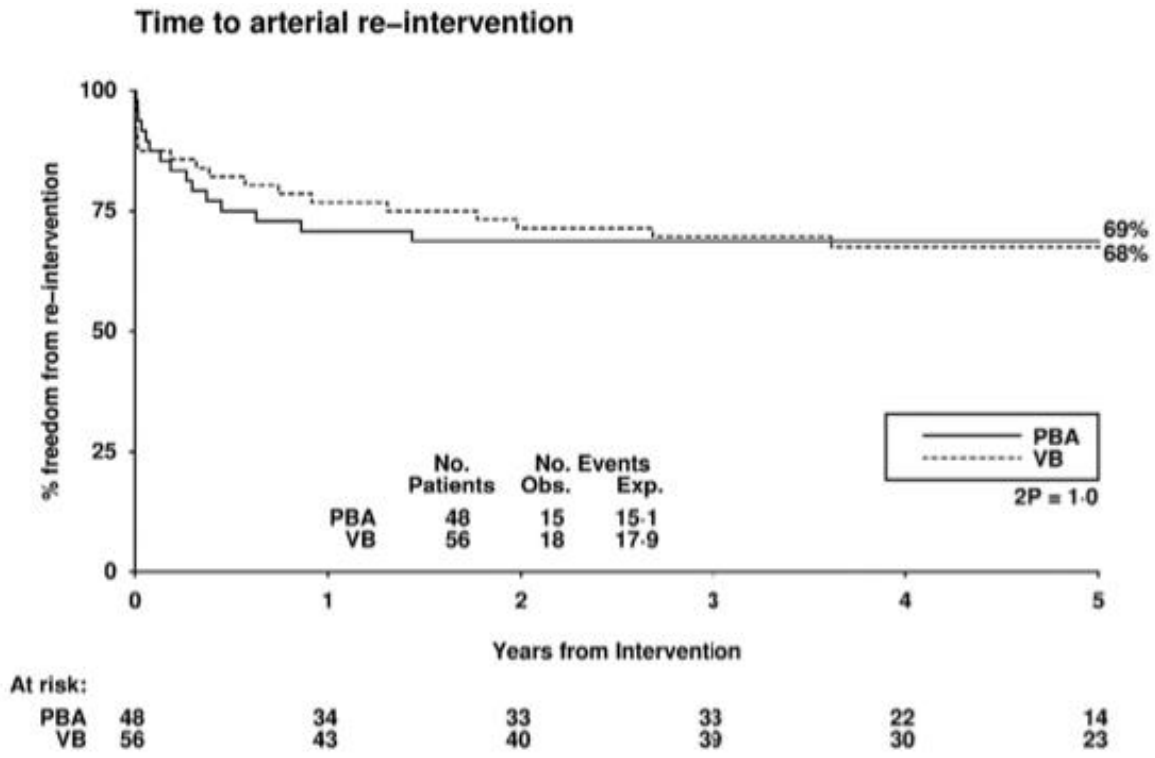
Figure 2.1.3 Overall Survival in the BASIL-1 infrapopliteal subgroup analysis



Overall survival. HR 0.60, 95% CI 0.36-1.02, p= .06.

Removing patients with prior arterial intervention from the analysis did not have any effect on outcome in terms of AFS (p= .5) or OS (p= .3). Similarly, when viewed as a whole cohort, patients with IP disease with prior intervention did not demonstrate significantly poorer AFS than patients with de novo lesions (p= .3). Time to arterial re-intervention (Figure 2.1.4) or time to major amputation (Figure 2.1.5) were similar in both arms, but clinically important halving or doublings of events could not be ruled out for either treatment.

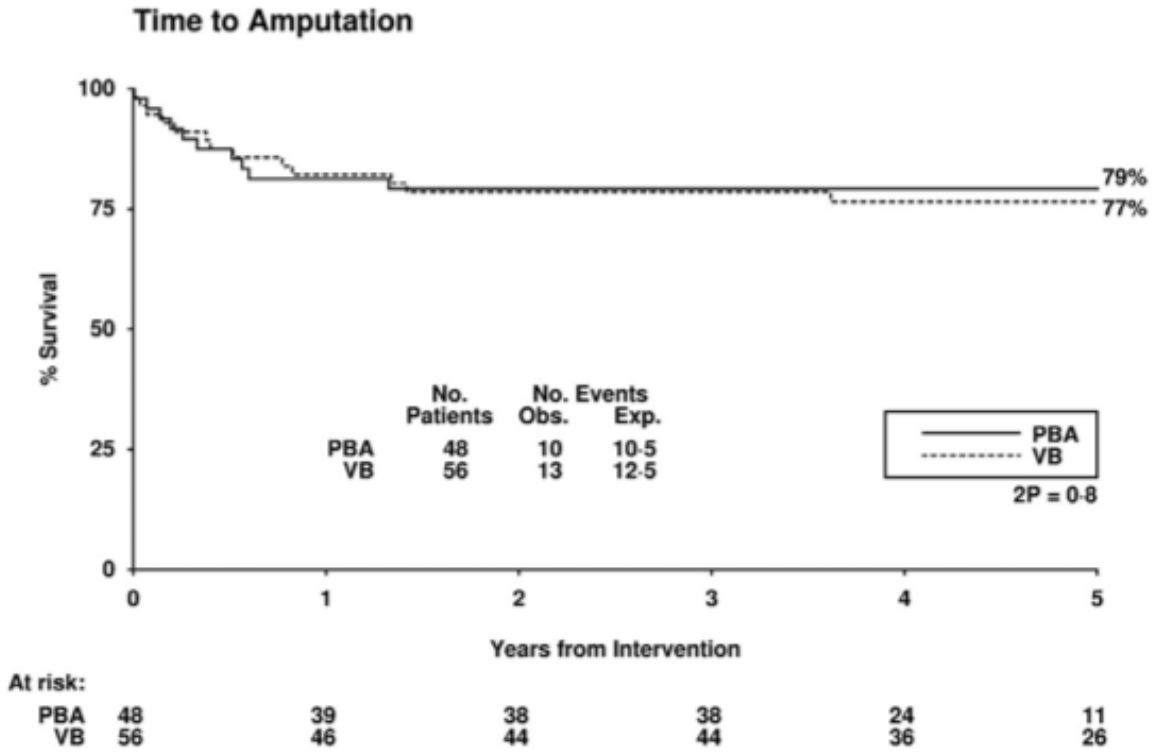
Figure 2.1.4 Time to arterial re-intervention in the BASIL-1 infrapopliteal subgroup analysis



Time to further arterial re-intervention. HR 1.01, 95% CI 0.51-2.00, p=1.0.

Mortality within 30 days of the index procedure was not significantly different (4 patients, 7% VB group vs. 1 patient, 2%, in the PBA group, p= .2). The most common causes of death were pneumonia and heart related disease (12 patients and 20 patients respectively) (Table 2.1.4).

Figure 2.1.5 Time to major amputation in the BASIL-1 infrapopliteal subgroup analysis



Time to major amputation. HR 1.10, 95% CI 0.48-2.49, p= .8.

Patients in the VB group were more likely to suffer morbidity within 30 days with more wound infections, sepsis and cardiovascular complications than patients in the PBA group (RR 2.86, 95% CI 1.25-6.53, p=.01) (Table 2.1.5).

Table 2.1.4 Causes of mortality in the BASIL-1 infra-popliteal subgroup analysis

Cause	**VB**	**PBA**	**Total**	**p value**
Pneumonia	5	7	12	.4
Other sepsis	2	3	5	.5
Malignancy	0	3	3	.06
"old age"	1	1	2	.9
Heart related disease	11	9	20	.9
Other vascular related disease (cerebrovascular accident, ruptured aortic aneurysm)	3	1	4	.4
Not known	5	7	12	.4
Total	27/56 (48%)	31/48 (65%)	58/104 (56%)	.09

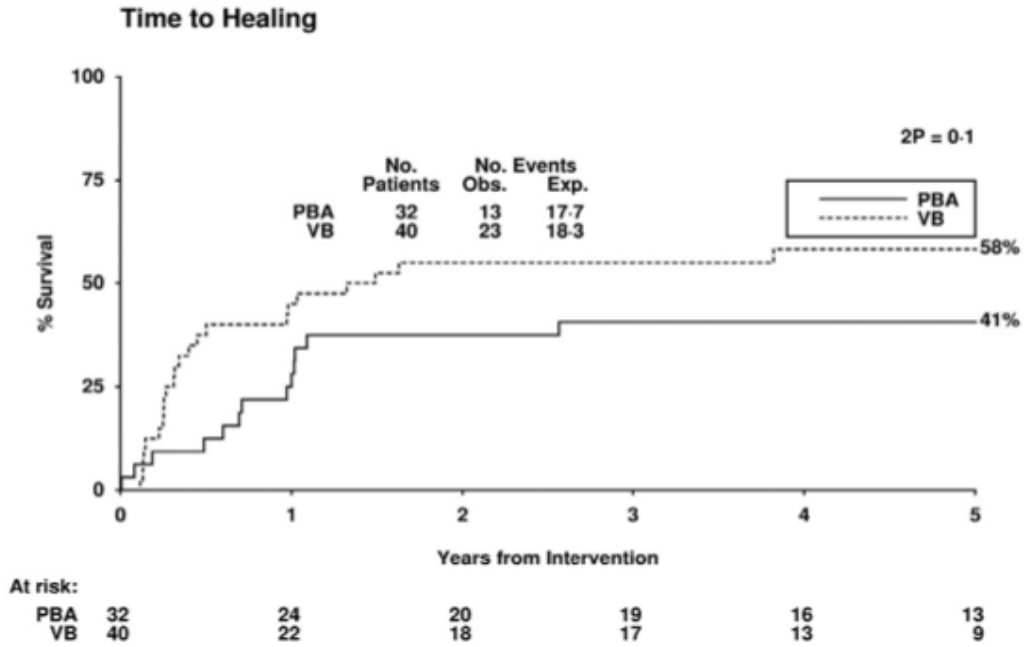
Table 2.1.5 Thirty-day morbidity in the BASIL-1 infra-popliteal subgroup analysis.

Cause	**VB**	**PBA**	**p value**
Bleeding	2 (4%)	1 (2%)	.7
Sepsis (urine, chest, *clostridium dificile* colitis)	4 (7%)	2 (4%)	.5
Wound infection	8 (14%)	2 (4%)	.08
Myocardial infarction	3 (5%) (all fatal)	0 (-)	.1
Cerebrovascular accident	1 (2%)	0 (-)	.4
Death from other causes	2 (4%)	1 (2%)	.7
Total	20/56 (36%)	6/48 (13%)	.01

In the VB group, nine patients had below knee amputation (BKA) and four had an above knee amputation (AKA) compared with six BKA and four AKA in the PBA group. Only one patient, who was in the VB group, had revision of a BKA to a higher level. Distribution of tissue loss was similar between the groups with most patients having gangrene or ulceration restricted to the digits (74% VB, 71% PBA). The median length of index hospital admission was significantly greater in the VB group (18 vs. 10 days, $p < .0001$) but there was no difference in total median hospital stay between randomisation and the primary endpoint (43.5 days VB vs. 42 days PBA).

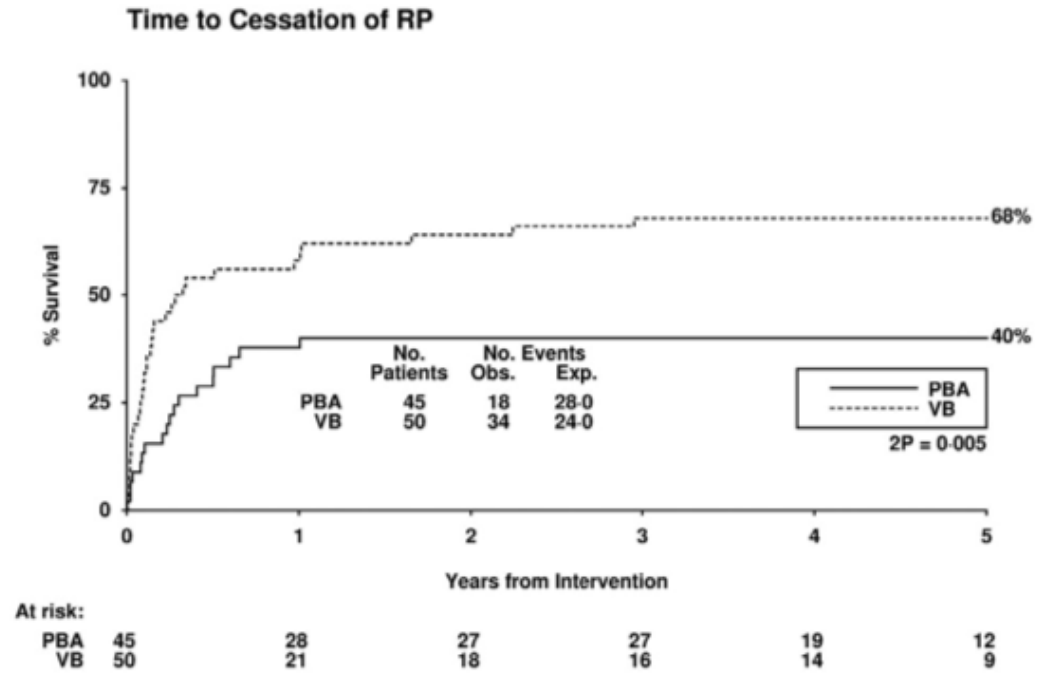
In the PBA and VB groups, 85% and 77% patients had pre and post-procedure ABPI measurements. The mean preintervention ABPI in the VB group was 0.53 (SD 0.38), which improved to 0.93 (SD 0.42) post intervention. In the PBA group mean pre-intervention ABPI was 0.43 (SD 0.27), which improved to 0.85 (SD 0.32). The mean improvement in ABPI was 0.42 (SD 0.36) and 0.37 (SD 0.38), respectively ($p= .18$). In terms of the quality of revascularisation, time to healing of tissue loss was 70% higher in favour of VB than PBA, although this was not statistically significant (HR 1.69, 95% CI 0.88-3.26, $p= .1$) (Figure 2.1.6). Relief of ischaemic rest pain was more than twice as common in the VB group (HR 2.19, 95% CI 1.27-2.78, $p= .005$) with more patients pain free at 5 years (Figure 2.1.7).

Figure 2.1.6 Time to healing of ischaemic tissue loss in the BASIL-1 infra-popliteal subgroup analysis.



Time to healing of ischaemic tissue loss. HR 1.69, 95% CI 0.88-3.26, p=.1.

Figure 2.1.7 Time to cessation of rest pain in the BASIL-1 infra-popliteal subgroup analysis



Time to cessation of rest pain. HR 2.19, 95% CI 1.27-3.78, p= .005.

Eight (17%) people in the PBA group went on have bypass compared with eight people (14%) in the VB group who went on to have PBA. Patients who underwent primary angioplasty that failed and went on to VB had no differences in AFS compared with patients undergoing primary VB. Likewise, no difference in AFS was seen in patients who underwent primary VB and went on to have secondary PBA.

Quality of Life Measures

Quality of life data is presented in Table 2.1.6. Quality of life improvements, in terms of mean overall VascuQoL score were seen in both groups from baseline to 3-months (VB 2.90 to 4.67, PBA 2.76 to 3.95). According to further analysis from The Supervised Exercise or Angioplasty for Intermittent Claudication Due to an Iliac Artery Obstruction (SUPER) study an improvement in the range of 1.19-1.66 is deemed clinically significant[92] (VB 1.77 vs. PBA 1.19). These improvements were sustained out to 12-months (VB 4.42 vs. PBA 4.09). Positive improvements were seen in both cohorts in all VascuQoL domains at 3-months. Both groups also demonstrated almost identical improvements in EQ 5D index at 3 months (VB Baseline 0.64, 3-months 0.72 vs. PBA Baseline 0.64, 3-months 0.71). Again, these improvements persisted out to 12-months (VB 0.73 vs. PBA 0.70). Interestingly, despite improved VAS scores at 3-months those undergoing PBA reported a negative drift back toward baseline at 12-months (PBA mean VAS at; Baseline 49.9, 3-months 58.1, 12-months 53.6) although the 12-month reported mean was still higher than baseline.

Table 2.1.6 Quality of Life measures in the BASIL-1 infra-popliteal subgroup analysis

	Baseline Mean (SD)		*3-Months Mean (SD)*		*6-Months Mean (SD)*		*12- Months Mean (SD)*	
Health Domain	**PBA (n=42, 87.5%)**	**VB (n=51, 91.1%)**	**PBA (n=34, 70.8%)**	**VB (n=39, 69.6%)**	**PBA (n=25, 52.1%)**	**VB (n=31, 55.6%)**	**PBA (n=18, 37.5%)**	**VB (n=28, 50.0%)**
VascuQoL								
Activity	2.24 (0.97)	2.39 (1.10)	3.14 (1.23)	3.92 (1.31)	2.93 (1.01)	3.69 (1.61)	3.02 (1.20)	3.79 (1.50)
Symptoms	3.51 (1.44)	3.87 (1.24)	4.88 (1.21)	5.47 (1.14)	4.56 (1.09)	5.18 (0.98)	4.96 (1.16)	5.14 (1.37)
Pain	2.28 (1.27)	2.50 (1.26)	4.13 (1.78)	4.86 (1.61)	3.76 (1.61)	4.33 (1.74)	4.32 (1.95)	4.54 (1.73)
Social	2.99 (1.70)	2.97 (1.83)	4.00 (1.87)	4.41 (1.71)	3.42 (1.73)	3.97 (1.68)	4.14 (1.88)	4.25 (1.73)
Emotional	3.17 (1.35)	3.14 (1.51)	4.24 (1.59)	5.04 (1.56)	4.19 (1.59)	4.75 (1.45)	4.69 (1.51)	4.71 (1.61)
Overall	2.77 (1.04)	2.90 (1.11)	3.95 (1.28)	4.67 (1.21)	3.72 (1.09)	4.35 (1.32)	4.10 (1.17)	4.42 (1.34)
EuroQoL-5D								
EQ-5D index	0.64 (0.07)	0.64 (0.07)	0.71 (0.12)	0.72 (0.11)	0.66 (0.11)	0.71 (0.12)	0.70 (0.11)	0.73 (0.14)
VAS	49.9 (22.0)	50.6 (22.1)	58.1 (17.1)	62.8 (19.2)	51.1 (20.9)	62.0 (22.4)	53.6 (21.5)	63.6 (16.8)

2.1.5 Discussion

Despite being underpowered, this analysis of the subgroup of IP patients receiving revascularisation for CLTI provides some thought-provoking evidence. Although the clinical endpoint analysis did not reach statistical significance there appears to be a positive, clinically

important limb salvage and survival advantage in favour of VB in this patient group despite a higher rate of smoking and previous myocardial infarction. In terms of OS there was almost a significant difference favouring VB, this may in part, be explained by the higher proportion of patients with IHD in the PBA group. Treatment success was also worse in those undergoing PBA which may have also impacted on long-term survival.

Clinical effects in terms of healing of ischaemic wounds were difficult to compare because of lack of detailed information regarding wound severity, depth, extent, or presence of infection. Owing to the data available, it was not possible to apply a validated, robust wound scoring system to describe differences, if any, in terms of extent of tissue loss between intervention groups. From the information available (anatomical location of tissue loss and time to complete healing) there was a trend towards improved healing rates in the VB group, although this was not statistically significant. Time to cessation of rest pain from primary intervention was significantly less in the VB group. This suggests that the 'quality' of revascularisation from VB may have been better. With regards to pain, no validated pain scoring system was used in the trial. Patients were simply asked at each visit if their pain was worse, the same, better or gone entirely. It is difficult therefore, to quantify the magnitude of this effect objectively.

It is accepted that such results should be interpreted with caution given the BASIL-1 trial was not powered to demonstrate treatment effects in the IP subgroup. Results from this study are however thought provoking and demonstrate the need for further higher quality evidence in this patient subgroup. It is also pertinent to note that despite higher 30-day morbidity in the VB group this did not correlate with poorer limb salvage or mortality. Increase in morbidity did, however, lead to a longer inpatient stay during the index admission.

In both groups the median length of hospital stay on index admission was high, the BASIL-1 trial accurately recorded the standard of care for CLTI patients in the UK at that point in time.

This was largely because most patients with CLTI were managed as an emergency rather than electively and a high proportion had tissue loss (approximately 70% in both groups), which often leads to complex social and wound management issues.

Interestingly, there was little or no difference in the length of time spent in hospital between the two groups from randomisation to primary endpoint, suggesting that the early advantage of a shorter length of stay in patients undergoing PBA is lost over a longer period when examining all-cause admissions. This cannot be accounted for by re-intervention alone, as this was broadly similar in both groups. The increased mortality in the PBA group may in part explain this, it is however unclear from the present data definitive reasons for this.

In both groups, treatment success was arguably low (VB 86% vs. PBA 73%). The original trial analysis was performed on an intention-to-treat analysis. At the time of randomisation, patients were deemed suitable for either intervention based on adequate radiographic assessment and clinical equipoise between both revascularisation strategies. However, in some patients randomised to VB on exploration of the target vessel, the distal bypass vessel was occluded or not suitable for surgical anastomosis. This would represent a similar situation to a failure or inability to cross a target lesion in the PBA group. The trial was designed to be pragmatic and to reflect variations in practice and assessment throughout the UK as no specific guidelines or evidence were available at the time of the BASIL-1 trial, even now with recent European guidelines[93] practices in imaging assessment and treatment methods vary widely. In this way, technical failure in both groups may not be an equal comparison, given that bypass grafts that failed within 24 hours were included as 'treatment failure', whereas the quality control regarding early endovascular treatment failure is unclear from the current available data.

In both groups quality of life domains were improved at 3-months and mostly these improvements were sustained out to 12-months except VAS in PBA patients which saw a

decrease in score toward baseline at the same timepoint. Overall VascuQoL scores improved to a level congruent with 'clinical significance' in a reported study, although this was in patients with intermittent claudication and not CLTI. These results, however, must be interpreted with caution. Quality of life questionnaire completeness diminished with time significantly in both groups (BS 50.0% vs. PBA 37.5% at 12-months). These 'missing' data are somewhat explained by attrition due to death, however despite this, many did not complete questionnaires past 3-months in both cohorts. This may have led to some reporting bias, in that those with the poorest outcomes and likely quality of life, did not complete the questionnaires leading to a more positive outlook.

The BASIL-1 trial has been criticised by some regarding generalisability, approximately 30% of screened subjects were randomised into the trial. This trend is seen in current clinical trials in patients with CLTI as patients present with heterogeneous patterns of anatomical disease, which can make comparisons and equipoise between treatment strategies a barrier to recruitment and inclusion despite a clear lack of evidence to support a first revascularisation treatment strategy.

CLTI remains a significant global problem[8,94]. Up to 50% of patients with CLTI will have significant IP disease and this proportion may be increasing due to the rising prevalence of diabetes and chronic kidney disease[95]. Unfortunately, the evidence base underpinning the management of CLTI resulting from IP disease remains extremely limited[24–28]. Present data indicate that it is far from clear that patients with CLTI who require IP revascularisation and who are suitable for VB should have BET as their primary procedure. The technical and clinical failure rate with IP PBA was high; whether this would be materially lower in current practice leading to improved clinical outcomes is a subject of ongoing research.

In conclusion, current data reconfirm the need for further publicly funded, unbiased, pragmatic RCTs, such as BASIL-2[12] and BEST-CLI[33] to compare clinical and cost effectiveness of IP VB and BET in patients suitable for both interventions. Ethical approval was granted as part of the BASIL-1 trial.

2.1.6 Limitations

Clearly this subgroup analysis of patients receiving IP revascularisation for CLTI has limitations. As stated previously, the BASIL-1 trial was powered to show a significant difference in amputation free survival based across the whole cohort, not just the 25% with IP disease. It is however interesting that, statistically speaking the direction of effect consistently favours a bypass first strategy, even if not significant in terms of "p-value". The analysis represents a post-hoc review of prospectively collected data from original trial case-report forms. Given that the BASIL-1 trial is now over a decade old, reporting standards and more contemporaneous published data fields (such as patency, lesion morphology, WIfI scores[29]) were not available. Such data fields would have added to the analysis as it would allow direct comparisons with less heterogenous groups.

2.2 A COMPARISON OF OUTCOMES FOLLOWING INFRA-POPLITEAL PLAIN BALLOON ANGIOPLASTY IN THE BASIL TRIAL (1999-2004) AND IN A CONTEMPORARY SERIES (2009-2013)

This study aims to compare outcomes in patients undergoing IP, endovascular intervention in two cohorts separated by a decade. This builds on the work from the last chapter, where outcomes from the IP subgroup in BASIL-1 were examined. One criticism of BASIL-1 data and the paper published above was that the cohorts are over a decade old, disease patterns have changed, and patients are more co-morbid. Also, many would argue that endovascular technology, success rates (and one would assume outcomes) have improved dramatically since the period of time when BASIL-1 was conducted. Therefore, it would seem entirely appropriate to examine these endovascular outcomes from BASIL-1 using a modern cohort of patients receiving similar treatments.

2.2.1 Abstract

Objectives:

To compare outcomes in patients randomised to infra-popliteal (IP) plain balloon angioplasty (PBA) for chronic limb threatening ischaemia (CLTI) within the Bypass versus Angioplasty in Severe Ischaemia of the Limb (BASIL-1) trial with outcomes in consecutive patients undergoing IP PBA at a University academic vascular centre in the UK in a modern setting (Contemporary Series, CS).

Methods:

Individual patient data were obtained from prospectively gathered computerised BASIL-1 (48 patients) and CS databases (73 patients). All had a minimum of 3-years of electronic follow up.

The outcomes studied were amputation free survival (AFS), overall survival (OS), major (above ankle) limb amputation, arterial re-intervention, immediate technical success and length of hospital stay for index procedure and during the following 12-month period. Statistical analysis was performed using SAS v9.4 statistical package©.

Results:

The BASIL-1 and CS cohorts were well matched for gender, age, diabetes, previous stroke, myocardial infarction and arterial intervention, and presence of tissue loss. More BASIL-1 patients underwent concomitant treatment of the superficial femoral (SFA) (60% vs. 37%, p=.01) and above knee popliteal (60% vs. 34%, p=.005) arteries. No drug eluting technology was used in either cohort. Immediate technical success increased from 73% (BASIL-1) to 90% (CS) (p=.01). There was no difference in AFS (HR=1.00, 95% CI: 0.65 – 1.54, p=1.0), overall survival (HR=1.04, 95% CI: 0.66 – 1.62, p= .9), major amputation (HR=0.86, 95% CI: 0.37 – 1.97, p= .7) or re-intervention (HR=0.61, 95% CI: 0.29 – 1.27, p= .2). Median length of stay after the index intervention was significantly shorter in the CS (p= .02) as well as the number of days spent in hospital over the 12 months following intervention (p= .002).

Conclusions:

Despite a significant improvement in the immediate technical success of IP PBA between 1999-2004 and 2009-2013, there were no significant improvements in limb and mortality-based endpoints, however, in modern times, patients spend significantly less time in hospital. BASIL-1 data therefore remain relevant to contemporary practice.

2.2.2 Introduction

Traditionally, CLTI was treated by means of bypass surgery but, in recent years, despite a lack of level I evidence, a growing proportion of affected patients have been offered an endovascular first revascularisation strategy.

A recent systematic review[25] identified only a few randomised trials comparing the two strategies[9,96,97]; these studies were all performed around a decade ago and mostly consider the management of superficial femoral artery (SFA) disease. Currently, there is no "level 1a" evidence available to guide the treatment of CLTI patients who require infra-popliteal (IP) revascularisation. The UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA)-funded Bypass Versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) trial remains the only randomised comparison of a bypass first with an endovascular first revascularisation strategy for CLTI secondary to infra-inguinal disease[9] and found that, in those patients who survived for more than two years after randomisation, bypass surgery was associated with a better outcome in terms of overall (OS) and amputation-free survival (AFS). However, only around 25% of the patients in BASIL-1 underwent an IP intervention and it is often argued that, given the subsequent advances in endovascular technology and techniques, were BASIL-1 to be repeated, it might show a clear advantage for endovascular revascularisation, especially below the knee.

In order to address this major gap in the evidence base, the UK NIHR HTA-funded BASIL-2 trial was funded and randomised patients with CLTI who require an IP intervention to either an IP vein bypass first or an IP best endovascular therapy (BET) first revascularisation strategy. The trial completed recruitment in November 2020 and is currently in the follow up period. The NIH-funded BEST-CLI trial is also randomising IP CLTI patients in the US. Recruitment for

both trials was slower than expected as many vascular specialists were reluctant to randomise such patients.

To help define the grey area of equipoise for BASIL-2 we have examined outcomes following IP endovascular intervention in 48 patients randomised in BASIL-1 between 1999 and 2004 and 73 consecutive patients treated within a UK University academic vascular centre between 2009 and 2013 (contemporary series, CS).

2.2.3 Methods

Individual patient data were obtained from computerised, prospectively gathered BASIL-1 and CS databases. BASIL-1 and CS outcome data were censored at 1 July 2007 and 1 February 2017 respectively, so providing a minimum of three years follow-up for both cohorts. CS patients were taken from a computerised database of consecutive endovascular treatments performed for CLTI at a single, UK tertiary vascular centre. To align with the BASIL-2 trial methodology patients undergoing IP intervention to the same leg during the previous 12 months were excluded. The outcomes studied were amputation free survival (AFS), overall survival (OS), major (above ankle) limb amputation, arterial re-intervention, immediate technical success and length of hospital stay for the index procedure and during the following 12-month period.

It was not possible to examine anatomical outcomes such as primary patency, secondary patency and restenosis for two reasons; one, these outcomes were not routinely measured during the BASIL-1 trial and two, outside of a trial these outcomes are not measured at our centre as part of routine clinical practice. Patients undergoing endovascular treatment are followed up and managed according to symptoms and review of clinical status of the limb and are not routinely re-imaged with duplex ultrasound or similar. The need for arterial re-intervention was determined clinically by absence of tissue healing or lack of relief/return of ischaemic

symptoms. Bollinger scores[98] were recorded in the BASIL-1 trial and these compared with scores calculated by the author for the CS to document severity of disease.

Time to event analyses are presented over a 5-year period by using Kaplan-Meier plots and hazard ratios with 95% confidence intervals used to describe treatment effects comparing the CS outcomes with BASIL-1. For each Kaplan Meier curve estimate once the number at risk reaches less than 20% of the total cohort results should be interpreted with caution as survival estimates are likely to become less reliable. Differences between the cohorts in other outcomes were compared using t-tests, chi-squared and Wilcoxon Rank Sum tests according to the type and distribution of data. Statistical analysis was performed using SAS version 9.4. ©

Ethical approval was granted as part of the original BASIL-1 trial (https://doi.org/10.1186/ISRCTN45398889) and all subjects within the trial provided informed, written consent. Institutional Review Board was waived as the CS data was obtained and anonymised from data collected as part of routine clinical practice and was subject to local approval at the corresponding institution.

2.2.4 Results

BASIL and CS patients were reasonably well matched in terms of age, sex, previous cerebrovascular disease, diabetes, tissue loss, hypertension, antiplatelet use and a history of previous arterial intervention (>12 months prior to infra-popliteal endovascular treatment). There were some significant differences in other co-morbidities, statin therapy, site and distribution of tissue loss, pattern of disease, and the extent of disease treated (Tables 2.2.1 and 2.2.2).

Of note, more BASIL-1 patients underwent concomitant treatment of the SFA (60% vs. 37%, p=.01) and above knee popliteal artery (60% vs. 34%, p=.005). Bollinger scores were available for 44/48 patients in BASIL-1 and 70/73 patients in CS.

Table 2.2.1 Baseline demographics for comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL trial (1999-2004) and in a contemporary series (2009-2013).

	BASIL (n=48)	**CS (n=73)**	**p value**
Mean age - years (SD)	77.2 (7.3)	76.9 (10.2)	.8
Male sex (%)	32 (67%)	52 (71%)	.6
Comorbidities			
Mean serum creatinine mmol/l (SD)	126.6 (68.3) n=41	125.3 (123.4) n=73	.9
Stroke / Transient Ischaemic Attack (%)	8 (17%)	16 (22%)	.5
Myocardial Infarction (%)	14 (29%)	29 (40%)	.2
Angina (%)	10 (21%)	31 (42%)	.01
End stage renal disease (%)	0 (-)	7 (10%)	.03
Diabetes Mellitus (%)	23 (48%)	45 (62%)	.1
Insulin dependent Diabetes Mellitus (%)	8 (35%)	17 (38%)	.7
Clinical Presentation			
Tissue loss (%)	41 (85%)	56 (77%)	.2
Site of tissue loss (single patient may have multiple sites)			
Hallux (%)	27 (56%)	24 (33%)	.02
Other toes (%)	29 (60%)	21 (29%)	.001
Forefoot (%)	10 (21%)	11 (15%)	.4
Hindfoot (%)	7 (15%)	8 (11%)	.5
Ankle (%)	9 (9%)	3 (4%)	.02
Above ankle (%)	1 (2%)	14 (19%)	.01
Medical therapy			
Antiplatelet agent (%)	30 (63%)	52 (71%)	.3
Dual antiplatelet therapy (%)	3 (6%)	19 (26%)	.006
Antihypertensive agent (%)	38 (79%)	58 (79%)	.3

Statin therapy (%)	15 (31%)	50 (68%)	<.0001
Formal anticoagulation (warfarin etc.) (%)	9 (19%)	5 (7%)	.05
Previous Intervention			
Total (%)	12 (25%)	16 (22%)	.7
Endovascular (%)	7 (15%)	11 (15%)	.9
Surgical (%)	6 (13%)	3 (4%)	.09
Bollinger Scores			
Mean Total score	94.9	92.5	.6
Mean Femoro-popliteal segment score	26.4	15.9	.001
Mean Infra-popliteal segment score	68.4	76.6	.03
Mean Number of segments scored	12.6/13	12.3/13	.07

Total angiographic scores were equivalent between the two groups (94.9 BASIL vs. 92.5 CS, p=.6), however patients in BASIL-1 had more severe disease burden in the femoropopliteal segment (26.4 vs 15.9, p=.001) and had less severe disease in the infrapopliteal segment (68.4 vs 76.6, p=.03) when compared to the CS. Due to a lack of data for some patients it was not possible to compare the two cohorts in terms of the SVS Wound Ischaemia Foot infection (WIfI) score[29].

Immediate procedural technical success, defined by the operator as successful initial revascularisation of the target vessel(s) on post-procedural angiography as in the original BASIL-1 trial, was significantly higher in the CS (90% vs. 73%, p=.01). Technical failure in both cohorts was largely due to an inability to cross the target lesion (21% BASIL-1 vs 5% CS); other reasons given were residual stenosis/recoil, distal embolism, and procedure abandoned at patient request.

Morbidity to 30 days was similar in both groups (Table 2.2.3) (13% BASIL-1, 14% CS). Bleeding complications were low in both cohorts (2% BASIL-1, 1% CS). However, 2 of 4 stents placed in SFA thrombosed. Median length of stay for the index intervention was

significantly shorter in the CS group (5 vs 10 days, p=.02). The median number of days spent in hospital over the 12 months following intervention was fewer in the CS group (13 vs 38, p=.002).

There were no significant differences in AFS (HR=1.00, 95% CI: 0.66-1.54, p=1.0), (Figure 2.2.1) OS (HR=1.04, 95% CI: 0.66-1.63, p=.9) (Figure 2.2.2), re-intervention (HR=0.63, 95% CI: 0.31-1.26, p=.2) (Figure 2.2.3) or major (above ankle) amputation (HR=0.86, 95% CI: 0.38-1.96, p=.7) (Figure 2.2.4) between the two cohorts. At the censor date 35% BASIL-1 and 30% CS were still alive.

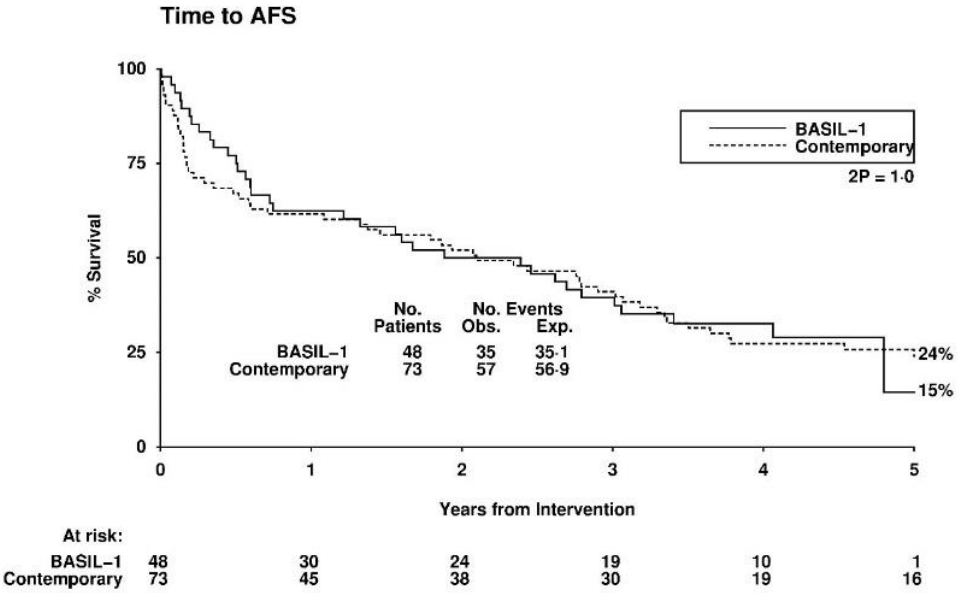
Table 2.2.2 Details of endovascular treatments in comparison of outcomes following infrapopliteal plain balloon angioplasty in the BASIL trial (1999-2004) and in a contemporary series (2009-2013)

		Number (%)		p value
		BASIL Cohort N=48	Contemporary cohort (CS) N=73	
Arteries treated	Superficial Femoral	29 (60%)	27 (37%)	.01
	Above Knee Popliteal	29 (60%)	25 (34%)	.005
	Below Knee Popliteal	28 (58%)	33 (45%)	.2
	Tibio-peroneal Trunk (TPT)	4 (8%)	26 (36%)	.0007
	Posterior Tibial	9 (19%)	16 (22%)	.7
	Peroneal	25 (52%)	18 (25%)	.002
	Anterior Tibial	19 (40%)	27 (37%)	.8
	Dorsalis Pedis	1 (2%)	1 (1%)	.8
Number of IP vessels treated	TPT most distal target	3 (6%)	18 (25%)	
	1 vessel	37 (77%)	49 (67%)	
	2 vessels	8 (17%)	6 (8%)	
	3 vessels	0 (-)	0 (-)	.02
Type of disease treated	Occlusive	36 (75%)	41 (56%)	.04
	Stenotic	25 (52%)	50 (68%)	.07
	Combination	13 (27%)	18 (25%)	.8
PBA and stent use	PBA only	47 (98%)	70 (96%)	.1
	PBA + Bail out BMS	1 (2%)	4 (5%)	.4
Technical Failure	Inability to cross lesion	10 (76%)	4 (57%)	
	Residual stenosis	1 (8%)	1 (14%)	
	Embolism	1 (8%)	2 (29%)	
	Abandoned at patient request	1 (8%)	0 (-)	
	Total technical failure	13/48 (27%)	7/73 (10%)	.01

Table 2.2.3 Thirty-day morbidity in comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL-1 trial (1999-2004) and in a contemporary series (2009-2013).

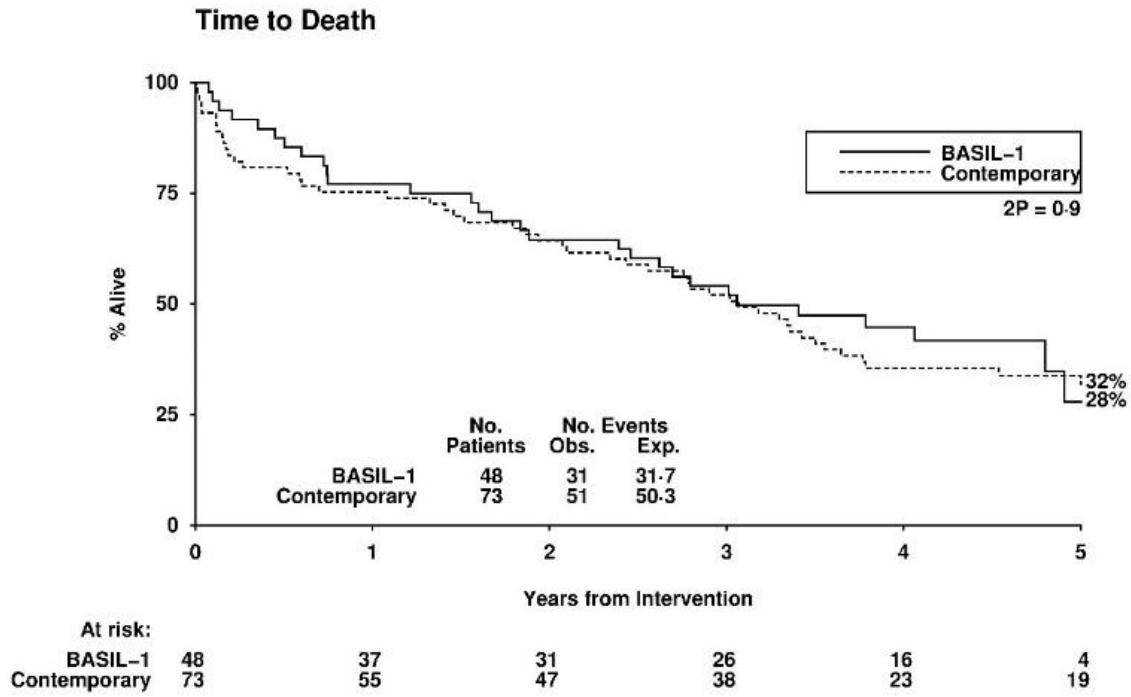
Cause	**BASIL cohort**	**Contemporary cohort (CS)**
Bleeding	1 (17%)	1 (10%)
Sepsis (urine, chest, CD colitis)	2 (33%)	0 (-)
Wound Infection	2 (33%)	0 (-)
Myocardial Infarction	0 (-)	4 (40%)
Pulmonary Embolism	1 (17%)	2 (20%)
Acute stent occlusion	0 (-)	2 (20%)
Death from other causes	0 (-)	1 (10%)
Total	**6/48 (13%)**	**10/73 (14%)**

Figure 2.2.1 Amputation Free Survival in comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL-1 trial (1999-2004) and in a contemporary series (2009-2013).



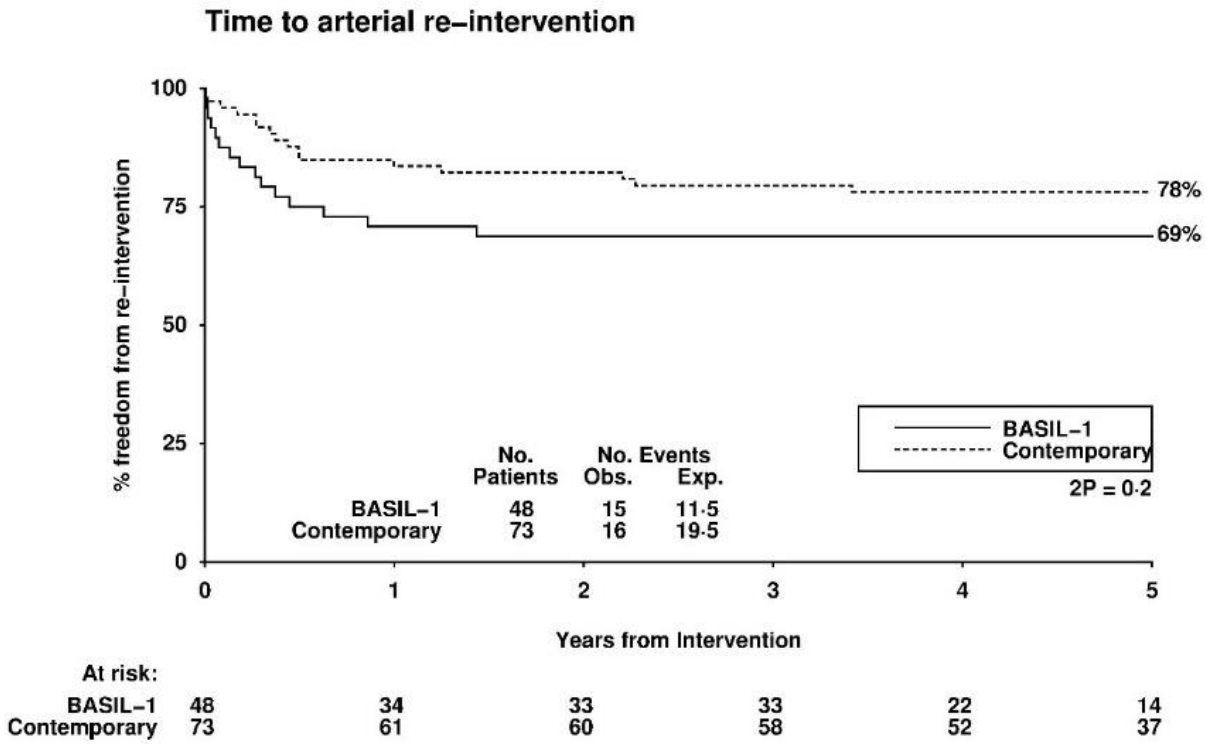
Amputation Free Survival. HR=1.00, 95% CI: 0.66-1.54, p=1.0

Figure 2.2.2 Overall Survival in comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL-1 trial (1999-2004) and in a contemporary series (2009-2013).



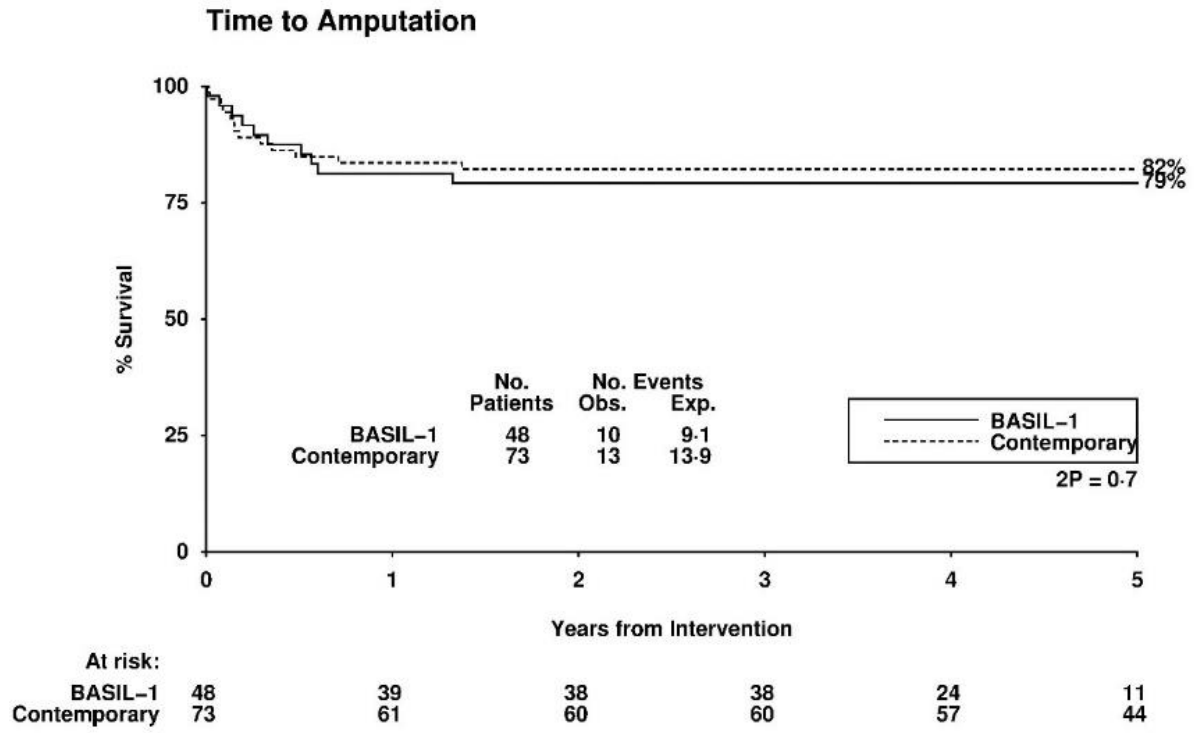
Overall Survival. HR=1.04, 95% CI: 0.66-1.63, p=.9

Figure 2.2.3 Time to arterial intervention in comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL-1 trial (1999-2004) and in a contemporary series (2009-2013).



HR=0.63, 95% CI: 0.31-1.26, p=.2

Figure 2.2.4 Time to major amputation in comparison of outcomes following infra-popliteal plain balloon angioplasty in the BASIL-1 trial (1999-2004) and in a contemporary series (2009-2013).



Time to major amputation. HR=0.86, 95% CI: 0.38-1.96, p=.7

Most deaths were cardiovascular (stroke, myocardial infarction, cardiac failure, sudden cardiac death) (32% BASIL vs. 31% CS, p=0.9); other common causes were pneumonia (23% BASIL-1 vs. 18% CS) and malignancy (10% BASIL-1 vs. 6% CS). A definitive cause of death could not be established in 29% of BASIL-1 and 23% of CS patients.

In terms of re-intervention, although non-significant in terms of all arterial re-intervention more patients in BASIL underwent "bail-out" vein bypass (16.6% vs. 9.6%) whilst similar proportions of patients in both cohorts had repeat PBA (8.3% BASIL-1 vs. 9.6% CS).

2.2.5 Discussion

The main finding of the present study is that despite a significant improvement in immediate technical success, there were no significant differences in important outcomes between BASIL (1999-2004) and CS (2009-2013) patients undergoing primary IP endovascular revascularisation, and event rates were comparable.

We accept that the CS cohort is non-randomised (although consecutive cases were used), and therefore, some of the results seen are prone to selection bias. However, we feel it remains of interest and value that the survival curves for both AFS and OS are almost identical despite the separation in time and likely advances both in technical ability and equipment. Immediate technical success, as previously described, was measured subjectively by the operator at the time of procedure and was documented when target vessel patency had been achieved angiographically to reflect the methodology of the BASIL-1 trial, making comparisons equivalent. All angiograms and interventional reports were reviewed by two authors (MP, HOBD) for accuracy; any discrepancies were discussed and clarified with the senior author (AWB). In both cohorts we accept that a more objective measure of patency is preferable, however this was not possible in the confines of this study.

BASIL-1 patients were more likely to have multilevel occlusive disease, and this may explain the lower rate of technical success particularly regarding the ability to cross the target lesion. The 90% technical success rate seen in the CS group is comparable to modern standards as seen in recent systematic review[75]. CS patients tended to be more comorbid (although not older) with a higher prevalence of chronic kidney disease, end stage renal disease and angina pectoris and this may explain why greater technical success did not translate into better long-term outcomes. Most patients in both cohorts underwent intervention to a single crural vessel. Whether

attempting to treat multiple IP vessels results in better outcomes is currently unknown as the extent to which the use of drug eluting technologies may have influenced clinical outcomes.

The shorter length of index hospital in the CS group may be accounted for by an increase "day case" procedures which in the UK has been largely driven by a shortage of hospital beds. However, whether outpatient treatment of CLTI is appropriate is an area of considerable controversy. Despite this, the significantly less time spent in hospital both at index admission and in the following 12-months is clearly beneficial in terms of cost to health care providers in the CS. Although there was improvement in best medical therapy between the BASIL and CS cohorts, there was no apparent improvement in limb salvage or cardiovascular morbidity and mortality. To demonstrate the impact of medical therapy on outcomes relevant to CLTI intervention a much larger cohort of patients would be required. Given the cohort is relatively small compared to most studies examining the impact of medical therapy it is therefore prone to type 2 error in this respect. It is difficult to draw conclusions on the effectiveness of medical therapy in this setting.

The results of this study indicate some uncertainty as to differences, if any, between the two cohorts. One limitation of the data is that the sample size in both cohorts is relatively low and has led to wide confidence intervals in all outcome comparisons between the two cohorts. The study was not powered to demonstrate a significant difference between the groups, however the complete lack of any signal indicating improved survival is of interest given the decade separating the treatments, and the significant improvement in technical success. This may be accounted for by the fact that the CS patients had more severe disease in the IP segment than in BASIL-1 and though this did not impact on technical success, the impact on long-term patency is unclear. Although no firm conclusions can be drawn, the study confirms the need for further robust data to explore the role and benefits of PBA in the IP segment.

Drug eluting technology and adjunctive stenting is not widely accepted as the standard of practice in the UK (devices/technology are not currently recommended by The National Institute of Health and Care Excellence (NICE) at the time of writing)[22]. During the period of the CS (between 2009 and 2013) access to such technology was not widely available. We would argue that plain balloon angioplasty remains the standard of practice in patients with CLTI due to *de novo*, tibial lesions. Currently, there is no credible evidence to support claims to the contrary.

Whilst endovascular options in the IP segment are numerous, current evidence has yet to provide clinical or cost-effectiveness data that suggest PBA should be anything other than the standard of care. Trials comparing drug coated balloons (DCB) and PBA initially demonstrating a reduction in restenosis, target lesion revascularisation (TLR) and target vessel occlusion at 12-months (anatomical outcomes)[99]. Unfortunately, the more recent IN.PACT DEEP trial revealed a higher rate of major amputation compared to control (PBA)[79]. Pooled data comparing drug eluting stents (DES) has suggested more promising results. Katsanos et al, reported reduced restenosis, TLR, amputation and improved wound healing when compared to control (BMS or PBA), without any impact on mortality[100]. These findings have been corroborated[101], however, most would agree that trial numbers are small in selected centres and selected lesions and further clinical evidence is clearly required, particularly regarding DEB technology which as mentioned earlier in the introduction is at the time of writing under intense scrutiny owing to the publication of data suggested in increased mortality related to paclitaxel based devices[31].

The increasing trend of offering patients with CLTI endovascular treatment rather than bypass surgery is not evidence-based[102–104]. Indeed, data from BASIL-1 and other sources suggest that IP endovascular therapy should probably be reserved for those patients who cannot undergo

vein bypass[57]. Primary technical success of endovascular IP intervention (including stenting) has been reported as 56-100%, with a pooled estimate of 89.0% +/- 2.2%[24].

2.2.6 Limitations

It is acceptable to comment on the appropriateness of comparing modern retrospective data with a historical control from a randomised controlled trial. Methodologically this is flawed, however the current evidence available to address current knowledge gaps is clearly lacking. What we have demonstrated is that in two groups of patients separated by a decade with similar disease and characteristics who have received similar treatments have not shown any improvements in hard clinical endpoints. Whether hard endpoints such as amputation free survival and overall survival are an appropriate measure for this population is certainly of debate.

It may be acceptable for a patient to receive multiple interventions and no improvement in hard clinical endpoints despite improved technical success if there was a substantial benefit in terms of symptom control or quality of life. Unfortunately, the data to demonstrate this does not exist at the time of writing and this does not explain the sudden and rapid explosion in the use of endovascular technology in the developed world.

2.2.7 Conclusions

Justifying endovascular firstly vascular strategy based on improved technologies and techniques is not supported by our present data, where despite a significant improvement in technical success, there was no improvement in clinical outcomes between 1999-2004 and 2009-2013. However, we do accept that differences in the cohorts with longer, more complex lesions in BASIL-1 and a less fit population with more severe IP disease in the CS (more ESRD and IHD) may account for the differences or lack of in terms of outcome. It remains of interest

that despite these factors, the survival trajectories for this patient population are strikingly similar. Whatever argument this stimulates, further targeted evidence is clearly required to guide practice and randomised controlled trials, such as BEST-CLI (US)[33] and BASIL-2 (UK)[12] may help to define such treatment algorithms. This has been recognised by key peripheral arterial disease (PAD) expert groups both in the UK[22] and the US[105].

2.3 A COMPARISON OF CLINICAL OUTCOMES IN PATIENTS SELECTED FOR INFRA-POPLITEAL BYPASS OR PLAIN BALLOON ANGIOPLASTY FOR CHRONIC LIMB THREATENING ISCHAEMIA BETWEEN 2009 AND 2013

Previously in section 2.1 outcomes in a more historical cohort were examined finding improved would healing, a significant reduction in rest pain but at the expense of greater morbidity and index hospital stays for those who underwent IP vein bypass surgery. This section aims to explore similar outcomes in patients selected for either IP BS or IP BET in a more modern cohort of patients at HEFT UHB.

2.3.1 Abstract

Introduction

A published subgroup analysis of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial suggests that, in patients with chronic limb threatening ischaemia (CLTI) due to infra-popliteal (IP) disease, clinical outcomes are better following vein bypass surgery (BS) than after plain balloon angioplasty (PBA). The aim of the present study is to determine if clinical outcomes following IP revascularisation in our unit are concordant with those found in BASIL-1.

Methods

We retrospectively analysed prospectively gathered data pertaining to 137 consecutive CLTI patients undergoing IP PBA or BS in our unit between 2009 and 2013. We compared 30-day morbidity and mortality, days in hospital (index admission and out to 12-months), amputation free survival (AFS), overall survival (OS), limb salvage (LS), and freedom from arterial re-

intervention (FFR). Patient outcomes were censored on 1 February 2017, providing a minimum 3 years follow-up.

Results

Patients undergoing BS (73/137, 47%) tended to be younger, have less comorbidity, and were more likely to be on best medical therapy (BMT). BS patients spent more days in hospital during the index admission (9 vs 5, p=.003), but not out to 12 months (15 vs 13, NS). BS patients suffered more 30-day morbidity (36% vs 10%, p<.001), mainly due to infective complications, but not mortality (3.1% vs 6.8%, NS). AFS (p=.001) and OS (p< .001), but not LS or FFR, were better after BS.

Conclusions

CLTI patients selected for revascularisation by means of IP BS had better long-term outcomes in terms of AFS and OS, but not FFR or LS. Although we await the results of the BASIL-2 trial, current data support the BASIL-1 sub-group analysis which suggests that patients requiring revascularisation for IP disease should have BS where possible and that PBA should usually be reserved for patients who are not suitable for BS.

2.3.2 Introduction

Chronic limb threatening ischaemia (CLTI) is a growing global health and social care problem due to widespread tobacco use and the increasing worldwide prevalence of diabetes[13,14]. The condition remains associated with very poor outcomes in terms of major lower limb amputation (MLLA) and premature cardiovascular and all-cause mortality. The evidence base underpinning the management of CLTI is limited, especially with regard to revascularisation strategies, and particularly with regard to the infra-popliteal (IP) segment. The UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA)-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 remains the only published randomised controlled trial (RCT) to have compared infra-inguinal bypass surgery (BS) with plain balloon angioplasty (PBA) for CLTI[11].

In 2017, we published a BASIL-1 IP sub-group analysis that demonstrated a trend towards improved amputation free survival (AFS) and overall survival (OS) in those undergoing BS, and showed that BS was associated with highly significantly better quality of revascularisation than PBA in terms of relief of ischaemic rest pain[57]. However, the procedures were performed between 1999 and 2003 leading to suggestions that BASIL-1 outcomes are no longer relevant to current endovascular practice.

To further address the issue of preferred IP revascularisation strategies for CLTI, the UK NIHR HTA funded the BASIL-2 trial which compares IP vein BS with best endovascular treatment (BET) in patients presenting with CLTI who require IP revascularisation[12]. The BASIL-2 trial completed recruitment in autumn of 2020 and is currently in the follow-up phase, such that the final results are unlikely to be published until early 2024. In the meantime, there remains a large "grey area of clinical equipoise" regarding IP revascularisation strategies for CLTI.

The aim of the present study was to determine if important clinical outcomes following IP revascularisation in our unit (2009-2013) are concordant with those found in BASIL-1 (2009-2013) and, further, to encourage participation in BASIL-2.

2.3.3 Methods

This was a retrospective analysis of prospectively gathered hospital data pertaining to 137 consecutive CLTI patients selected for either IP PBA or BS in our unit between 1 June 2009 and 30 July 2013. Prior to revascularisation, all patients were discussed in a vascular multi-disciplinary meeting. Intervention was planned based on the availability of venous conduit, patient fitness, patient wishes and the technical possibilities following detailed imaging. We compared 30-day morbidity and mortality, length of hospital stays (for both index admission and out to 12-months), amputation free survival (AFS), overall survival (OS), limb salvage (LS), and freedom from arterial re-intervention (FFR). In addition to this, we compared AFS and OS in those that survived the primary hospital episode with the index limb intact.

As the data analysed were collected as part of normal routine clinical practice, ethical approval was not sought in accordance with advice from the UK National Research Ethics Service (http://www.hra-decisiontools.org.uk/ethics/). Patient outcomes were censored on 1 February 2017 so providing a minimum of 3 years follow-up. Continuous data are reported using mean or median values and compared using t-test or Mann-Whitney U test, depending on the characteristics of data distribution. Categorical data are compared using Fishers Exact or Chi^2 test. Time to event data were analysed using the Kaplan-Meier method and log-rank statistics presented as a hazard ratio and 95% confidence intervals (CI). For each Kaplan Meier curve estimate once the number at risk reaches less than 20% of the total cohort results should be interpreted with caution as survival estimates are likely to become less reliable. Statistical analysis was performed using R version 3.6.1 (2019-07-05)© 2019. The R Foundation for

Statistical Computing. Graphical illustrations presented were prepared using GraphPad Prism 8 software ver. 8.3.0, GraphPad Software, LLC©.

2.3.4 Results

Patients undergoing BS (64/137, 47%) tended to be younger with less comorbidity and were also more likely to be on best medical therapy (BMT) (Table 2.3.1). Patients undergoing PBA had a higher incidence of previous myocardial infarction (BS 10/64, 16% vs. PBA 29/73, 40%, p=.004) and were more likely to have diabetes (BS 27/64, 42% vs. PBA 45/73, 62%, p=.02). Although the number of patients with tissue loss in both groups was similar, the PBA patients tended to have more hindfoot involvement. A higher proportion of patients undergoing BS had undergone previous arterial intervention (BS 24/64, 38% vs. PBA 16/73, 22%, p=.04).

In those patients undergoing PBA, four also received a bare metal stent (BMS). No drug coated balloons (DCB) or drug eluting stents (DES) were used. Only six PBA patients had more than one crural vessel treated (Table 2.3.2). Immediate technical success (defined by the operator at the time of procedure) was 90%. In four cases it was not possible to cross the target lesion; two patients had distal embolism which resulted in loss of the target vessel; and one patient had a residual stenosis that was not amenable to stenting.

The majority of patients undergoing BS had great saphenous venous conduit (53/64, 83%) which was usually reversed (Table 2.3.3). Prosthetic material was used in nine patients (three prosthetic and six composite-sequential grafts). This is unlikely to reflect current UK clinical practice as since the final BASIL-1 report[11], prosthetic grafts for IP disease have largely been abandoned as a revascularisation option for most CLTI patients. Immediate technical success was 97%; two procedures were abandoned as the target crural vessel was judged unsuitable for bypass following surgical exposure. In five patients, the bypass failed within 30 days.

Thirty-day mortality was non-significantly worse in patients undergoing PBA (RR 2.19, 95% CI 0.44 – 10.91, 5 patients, 6.8% vs. 2 patients, 3.1% BS, NS). In both cohorts the most common causes of death were pneumonia, sepsis from other causes and cardiac disease (Table 2.3.4).

Table 2.3.1 Baseline Characteristics of patients selected for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.

	BS (n = 64)	**PBA (n = 73)**	**p value**
Mean and SD age (years)	73.2 (11.2)	76.9 (10.2)	.02
Male (%)	48 (75%)	52 (71%)	NS
Comorbidities			
Mean serum creatinine mmol/l (SD)	103.7 (112.5)	125.3 (123.4)	NS
Stroke / Transient Ischaemic Attack (%)	13 (20%)	16 (22%)	NS
Myocardial Infarction (%)	10 (16%)	29 (40%)	.004
Angina (%)	17 (27%)	31 (42%)	.05
End stage renal disease (%)	2 (3%)	7 (10%)	NS
Diabetes Mellitus (%)	27 (42%)	45 (62%)	.02
Insulin dependent Diabetes Mellitus (%)	10/27 (37%)	17/45 (38%)	NS
Clinical Presentation			
Tissue loss (%)	44 (69%)	56 (77%)	NS
Site of tissue loss (single patient may have multiple sites)			
Hallux (%)	19 (30%)	24 (33%)	NS
Other toes (%)	19 (30%)	21 (29%)	NS
Forefoot (%)	6 (9%)	11 (15%)	NS
Hindfoot (%)	1 (2%)	8 (11%)	.03
Ankle (%)	3 (5%)	3 (4%)	NS
Above ankle (%)	10 16%)	14 (19%)	NS
Medical therapy			
Antiplatelet agent (%)	55 (86%)	52 (71%)	.04
Dual antiplatelet therapy (%)	8 (13%)	19 (26%)	.04
Antihypertensive agent (%)	51 (80%)	58 (79%)	NS
Statin therapy (%)	57 (89%)	50 (68%)	.004
Anticoagulation (%)	13 (20%)	5 (7%)	.02
Previous Intervention			
Total (%)	24 (38%)	16 (22%)	.04
Endovascular (%)	17 (27%)	11 (15%)	NS
Surgical (%)	10 (17%)	3 (4%)	0.03

Table 2.3.2 Plain balloon angioplasty treatment details of patients selected for treatment between 2009 and 2013.

		No. (n=73)
Arteries treated	Superficial Femoral	27 (37%)
	Above Knee Popliteal	25 (34%)
	Below Knee Popliteal	33 (45%)
	Tibio-peroneal Trunk	26 (36%)
	Posterior Tibial	16 (22%)
	Peroneal	18 (25%)
	Anterior Tibial	27 (37%)
	Dorsalis Pedis	1 (1%)
Number of IP vessels treated	TPT most distal target	18 (25%)
	1 vessel	49 (67%)
	2 vessels	6 (8%)
	3 vessels	0 (-)
Type of disease treated	Occlusive	41 (56%)
	Stenotic	50 (68%)
	Combination	18 (25%)
Type of intervention	PBA	70 (96%)
	PBA + bare metal stent	4 (5%)
Technical Failure	Inability to cross lesion	4/7 (57%)
	Residual stenosis	1/7 (14%)
	Embolism	2/7 (29%)
	Abandoned at patient request	0 (-)
	Total technical failure	7/73 (10%)

Table 2.3.3 Bypass surgery treatment details of patients selected for treatment between 2009 and 2013.

		Number (n=64)
Conduit	Reversed vein (when vein used alone)	34 (53%)
	Non-reversed vein (when vein used alone)	19 (30%)
	Leg vein	46 (72%) Ipsilateral GSV 6 (9%) contralateral GSV
	Arm vein	1 (2%)
	Prosthetic	3 (5%)
	Composite Sequential	6 (9%)
	No bypass performed as distal target not patent	2 (3%)
Proximal anastomosis	Common femoral artery	51 (80%)
	Superficial femoral artery	5 (8%)
	Profunda femoris artery	0 (-)
	Above knee popliteal artery	5 (8%)
	Below knee popliteal artery	1 (2%)
Distal anastomosis	Tibioperoneal trunk	8 (12%)
	Posterior tibial artery 1/3	16 (25%)
	Posterior tibial artery 2/3	4 (6%)
	Posterior tibial artery 3/3	6 (9%)
	Peroneal artery 1/3	12 (19%)
	Peroneal artery 2/3	0 (-)
	Peroneal artery 3/3	2 (3%)
	Anterior tibial artery 1/3	9 (14%)
	Anterior tibial artery 2/3	2 (3%)
	Anterior tibial artery 3/3	1 (2%)
	Dorsalis pedis	2 (3%)
Technical failures	Early failure (<30 days)	5 (8%)
	Abandoned, no outflow vessel	2 (3%)
	Total technical failure	**7/64 (11%)**

Table 2.3.4 Cause of death in patients for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.

Cause	**BS (n = 64)**	**PBA (n = 73)**	**p value**
Pneumonia/Respiratory	4 (6%)	10 (14%)	NS
Sepsis (other causes)	2 (3%)	4 (5%)	NS
Malignancy	2 (3%)	3 (4%)	NS
Cardiac	3 (5%)	9 (12%)	NS
Acute Kidney Injury	2 (3%)	0 (-)	NS
Unknown	8 (13%)	16 (22%)	NS
Stroke	2 (3%)	4 (5%)	NS
Upper Gastrointestinal bleeding	1 (2%)	0 (-)	NS
"Old age"	0 (-)	2 (3%)	NS
Intracranial bleed	0 (-)	2 (3%)	NS
Venous thromboembolism	0 (-)	1 (1%)	NS
Total	**24/64 (38%)**	**51/73 (70%)**	**<.001**

Those selected for BS suffered more 30-day morbidity (RR 3.75, 95% CI 1.72 – 8.15, p<.001), mainly as a result of surgical site infection (SSI) and other causes of sepsis (Table 2.3.5). BS patients spent more days in hospital during the index admission (median 9 vs 5 days, p=.003), but not out to 12 months (median 15 vs 13 days, NS).

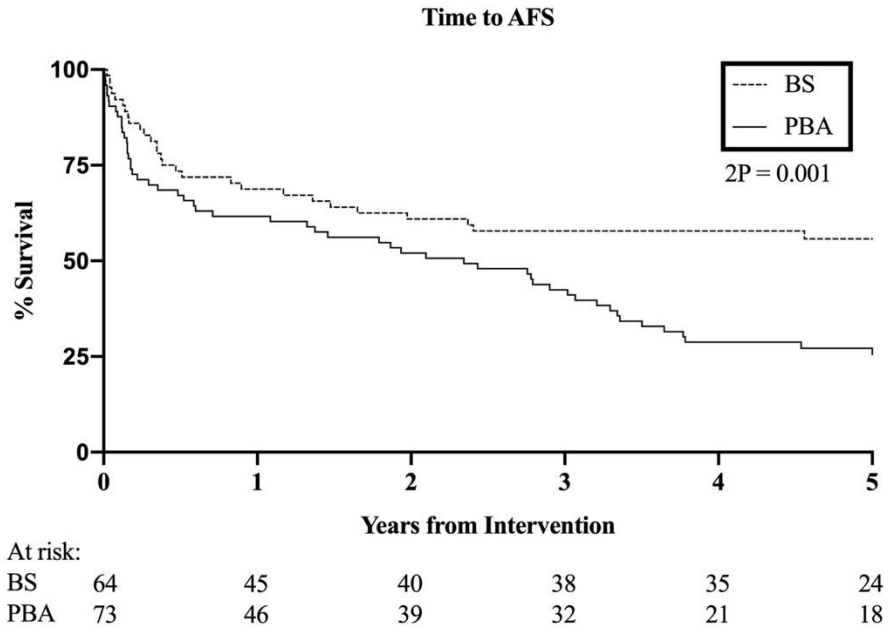
AFS was significantly better in those selected for BS (HR 0.50, 95% CI 0.33 - 0.76, p=.001**,** Figure 2.3.1). AFS after BS was estimated at 69%, 58% and 56% at 1, 3 and 5 years respectively and the mean AFS after BS was 4.6 (3.8 to 5.5, 95% CI) years. AFS after PBA was estimated at 62%, 42% and 26% at the same time points and the mean AFS after PBA was 2.8 (2.2 to 3.4, 95% CI) years.

Table 2.3.5 Peri-procedural (Thirty-day) morbidity in patients for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.

Cause	**BS (n = 64)**	**PBA (n = 73)**	**p value**
Bleeding	3 (5%) (1 CD IIIb)	1 (1%) (CD II)	NS
Sepsis (urine, chest)	7 (11%) (CD II)	0 (-%)	.004
Surgical site infection (SSI)	9 (14%) (6 CD II, 3 CD IIIb)	0 (-%)	<.001
Myocardial infarction / congestive cardiac failure	3 (5%) (2 CD II), 1CD V)	4 (5%) (1 CD II, 3CD V)	NS
Groin haematoma	3 (5%) (CD IIIb)	0 (-)	NS
Venous thromboembolism	1 (2%) (CD II)	2 (3%) (1/2 CD II) (1/2 CD V)	NS
Total	23/64 (36%)	7/73 (10%)	<.001

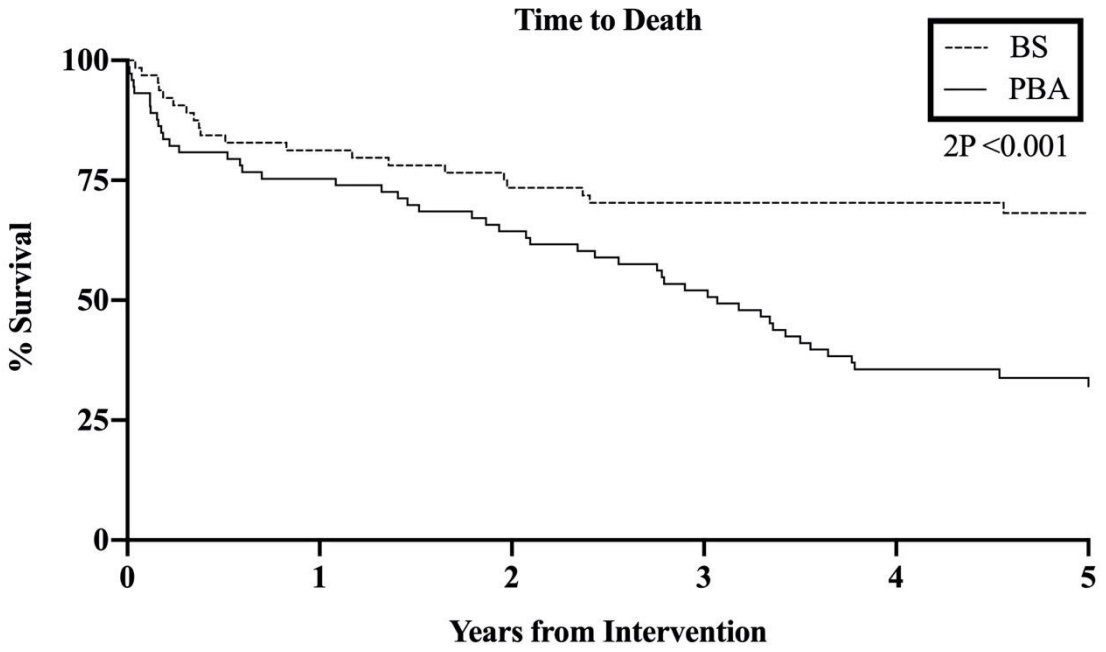
Abbreviations; CD – Clavien-Dindo[106]

Figure 2.3.1 Amputation Free Survival in patients selected for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.



OS was also significantly better in those selected for BS (HR 0.42, 95% CI 0.27 – 0.66, p<.001, Figure 2.3.2). OS following BS was estimated at 80%, 71% and 69% at 1, 3 and 5 years respectively, and the mean OS after BS was 5.6 (4.7 to 6.4, 95% CI) years. OS following PBA was estimated at 75%, 52% and 34% at the same time points, and the mean OS after PBA was 3.5 (2.9 to 4.1, 95% CI) years.

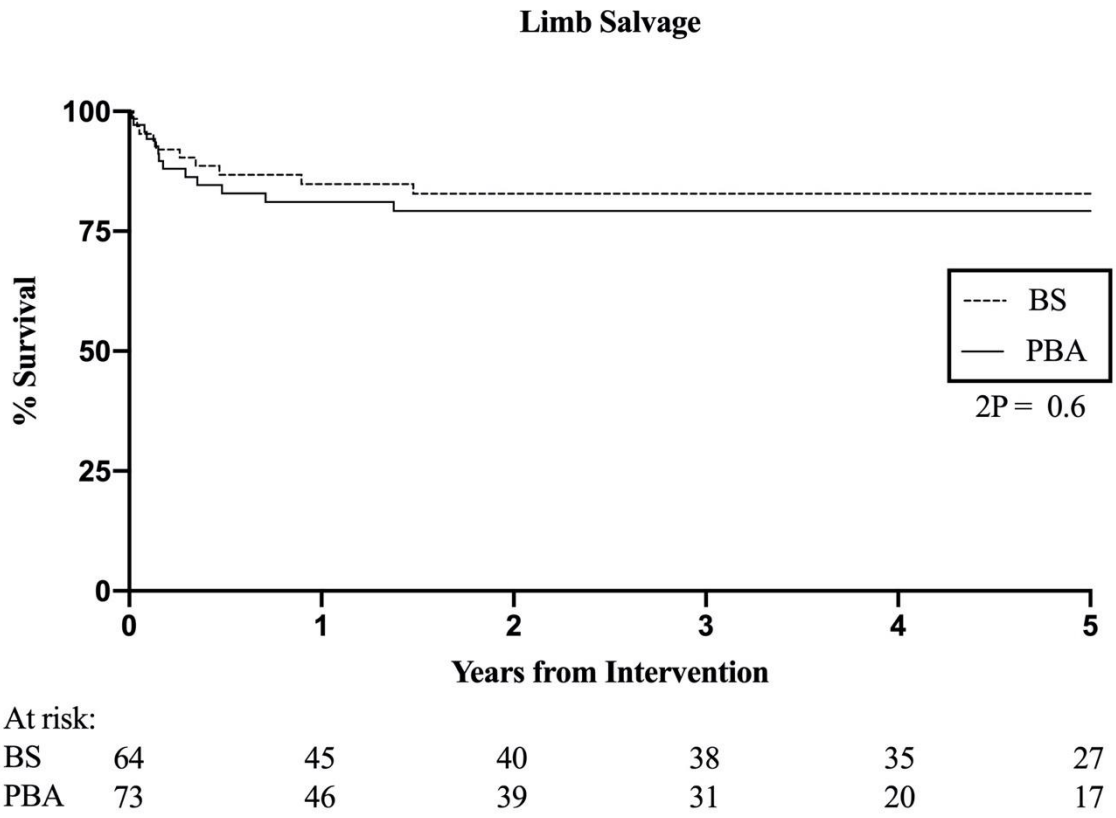
Figure 2.3.2 Overall Survival in patients selected for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.



At risk:						
BS	64	53	48	46	41	34
PBA	73	56	48	39	24	20

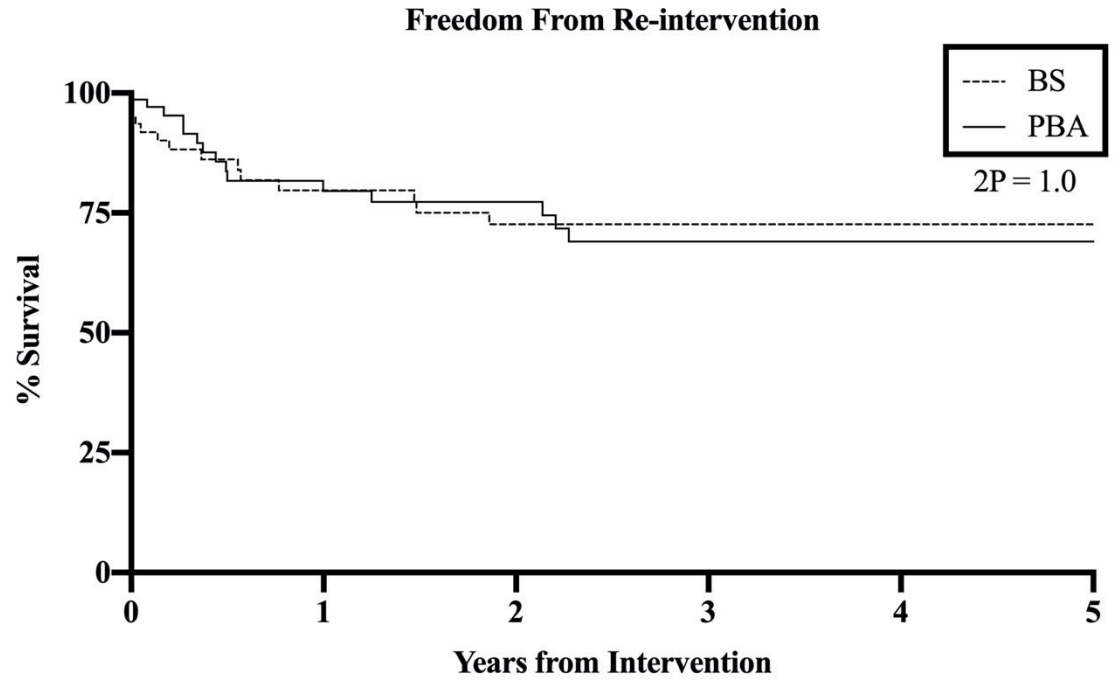
There was no significant difference in LS between BS and PBA (HR 0.80, 95% CI 0.35 – 1.81, p=.6, Figure 2.3.3). In the BS group, six patients had transtibial and four had transfemoral amputations. In comparison, seven of those undergoing PBA required transtibial and four had transfemoral amputations.

Figure 2.3.3 Limb Salvage in patients selected for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.



There was no significant difference in FFR between BS and PBA (HR 0.99, 95% CI 0.48 – 2.05, p= 1.0, Figure 2.3.4). Eight patients (12.5%) in the BS group required secondary bypass, whereas three (4.7%) went on to have PBA. Seven of those undergoing PBA (9.6%) had repeat PBA, and seven patients (9.6%) went on to have BS.

Figure 2.3.4 Freedom from re-intervention in patients selected for infra-popliteal bypass or plain balloon angioplasty between 2009 and 2013.



At risk:						
BS	64	36	32	30	27	19
PBA	73	38	30	22	13	11

Accounting for inpatient hospital death and amputation, 63 and 66 patients undergoing BS and PBA respectively were discharged from our vascular unit. Of these remaining patients, those undergoing BS had significantly better AFS (HR 0.54, 95% CI 0.35 – 0.84, p=.006) and OS (HR 0.46, 95% CI 0.29 – 0.74, p=.002) than those undergoing PBA.

2.3.5 Discussion

The main finding of the present study is that important clinical outcomes following IP BS and PBA in a non-randomised contemporary series of patients treated in our unit between 2009 and 2013 are very similar, both in absolute and relative terms, to those reported in patients recruited to the multi-centre BASIL-1 RCT between 1999 and 2003. In our series, patients undergoing BS did significantly better in terms of AFS and OS than those receiving PBA. The difference seen in AFS is mostly explained by late (after 2-years) mortality, given the extremely similar rates of limb salvage. This can be explained in part by the fact that patients in the BS group were younger and less comorbid. In BASIL-1 we demonstrated similar outcomes but to a much smaller degree of significance than we present here.

Patients in this contemporary series (CS) selected for BS had similar characteristics in terms of age and the presence of previous stroke related disease, myocardial infarction, end stage renal disease (ESRD) and diabetes to those patients in the BASIL-1 IP subgroup (B1). However, those undergoing PBA tended to have a higher burden of such co-morbidity.

One may argue that the number of IP revascularisations in a 50-month period is low, given the size of our vascular unit. In the last decade we have seen a shift in the presentation of disease. We performed a recent, large unpublished prospective cohort study that demonstrated that around 40% of patients who present with CLTI with significant IP disease are either too unfit for any intervention or have tissue loss and/or arterial disease that is beyond salvage. We hypothesize the causation of such presentations is the increasing burden of diabetes, end-stage renal disease and advancing age of the general population.

In terms of BMT, the prescription of statins in the current BS cohort had more than doubled when compared to the B1 BS patients (B1 39% vs. CS 89%). In the B1 subgroup, 75% of

patients undergoing BS were prescribed an antiplatelet agent; in the current BS cohort this was higher at 86%. Although improved rates of statin prescription were also seen in the current PBA cohort compared with the B1 PBA patients (68% vs 25%), rates were still much lower than in those undergoing BS. Only 58% of patients undergoing PBA in the B1 cohort were prescribed an antiplatelet agent. Although this had increased to 71% in our current cohort, this is still far from optimal and may have contributed to the poorer outcomes in this group. More rigorous follow up in the BS group (graft surveillance) provides an additional opportunity to reinforce the importance of BMT. Reduced outpatient contacts with the patients undergoing PBA may explain the difference in statin prescribing practice. The recorded increase in statin prescription is likely due to an increased awareness of the importance of BMT in the CLTI population which was further reinforced in 2012 by the National Institute of Health and Care Excellence (NICE) published Clinical Guideline on peripheral arterial disease (CG147)[22].

Disappointingly, the majority of patients (>80%) still present with tissue loss and this has remained unchanged since B1. It is difficult to know if the extent of tissue loss was different between these groups as the Society for Vascular Surgery (SVS) Wound Ischaemia Foot Infection (WIfI)[29] tool was not in use during either study period. Although patients in the PBA group presented with more tissue loss in the hindfoot, which may have contributed to their overall poorer outcomes.

We have previously reported a comparison of outcomes in the patients undergoing IP PBA in this cohort with similar patients in the B1 subgroup[58]. In that study we demonstrated that although patients were similar at baseline, patients undergoing IP intervention had a greater burden of FP disease in patients from the B1 cohort. Although PBA technical success was also somewhat better in our current IP cohort than B1, this did not appear to translate into any longer-term clinical benefit I in terms of AFS or OS.

Immediate technical success rates have improved since BASIL-1 for both BS (97% vs 86%) and PBA (90% vs. 73%). Our current technical success for patients undergoing IP PBA is comparable to results published in the literature[75]. This may be due to improved technologies, techniques and better patient selection.

Following PBA, seven patients (9.6%) went on to have salvage BS with vein. One may argue that this group of patients would have been better served with primary vein bypass. The implications of this and how this would have affected outcomes is a matter of speculation. It is likely that in this group of patients, some clinical equipoise was present between the two strategies. It is hoped that the results of the BASIL-2 trial[12] will aide decision making in this group of patients.

Patients in our current series spent less time in hospital than those a decade previously in B1. The length of index hospital admission was 50% lower in our recent cohort when compared to B1 (median BS 18 days vs. PBA 10 days) for both the BS and PBA groups. B1 patients also spent longer in hospital over the 12-months following intervention (a median of over 40 days).

AFS in B1 was estimated at 36% for BS and 15% for PBA out to 5 years. This was higher in our current series (BS 56% vs. PBA 25%). Trends in OS significantly improved in those undergoing BS (B1 49% vs. CS 68%) but not PBA (B1 28% vs. CS 32%) at the same time point. As discussed above, this may be due to better BMT seen in our current series although it is likely to be multifactorial. In those that survived, LS (approximately 80%) and FFR (approximately 70%) were similar to that observed for both BS and PBA in B1.

Interestingly, after removing patients that did not survive the index hospital admission or had an early amputation the significant differences in AFS and OS remained consistent, favouring those patients undergoing BS. As in BASIL-1, these differences are the greatest two years from

index intervention. This demonstrates that differences in survival are truly long-term as early death or amputation in either group of patients, who one may argue may have not been fit for intervention at all, did not impact the significance of the findings.

Peri-procedural (thirty-day) morbidity in the current series was very similar to that reported in B1. Thus, in the B1 BS group, 36% experienced a complication within 30-days and the majority of these were SSI and other forms of sepsis.

Unlike B1, the current cohort of patients was not randomised and so there will have been selection bias regarding the choice of revascularisation. However, what the data do show is that, if a patient was deemed fit enough for BS, then long-term AFS and OS were significantly better than after PBA. This supports the findings of the BASIL-1 trial overall[9] and the BASIL-1 IP subgroup analysis[58]. The unanswered question is how many patients who underwent PBA in the current cohort could, and perhaps should, have undergone BS instead and, if they had, would they have enjoyed a better longer-term outcome. Only randomised controlled trials that are free of selection basis can address these types of questions.

Use of drug coated balloons and drug eluting stents were not considered UK standard of care during the time of the study as there was no evidence of clinical and, in particular, cost-effectiveness[22]. The UK NICE was criticised for this stance at the time but, more recently, significant controversy has surrounded the use of such devices owing to meta-analyses [31,78] demonstrating an increase in all-cause mortality with paclitaxel devices. Following the publication of these data, paclitaxel-based devices were excluded from BASIL-2[12] and recruitment was paused in both the BASIL-3 trial[107] and SWEDE-PAD[108] trials. BASIL-3 reopened in September 2019 and completed recruitment in April 2021 and is currently pending the completion of follow-up data prior to reporting. The SWEDEPAD trials have also re-opened to recruitment but are yet to hit final targets as of September 2021.

The recently published Global Vascular Guidelines[13,14] recommend an individually tailored approach to revascularisation in patients with CLTI. BS is recommended for infrainguinal disease in average risk patients with a suitable venous conduit (expected peri-operative mortality of less than 5% or life expectancy >2years). However, these recommendations are based on the current best available evidence which is categorized by the GVG writing group as "Level C" (low). Going forward, it is very important that clinicians offer patients evidence-based revascularisation that is both clinically and, very importantly given that the greatest future CLTI burden is likely to be in low- and middle-income countries, cost effective. The results of the BASIL-2[12], BASIL-3 and BEST-CLI[109] randomised controlled trials are eagerly awaited.

2.3.6 Limitations

Numbers in both cohorts are relatively low, therefore any conclusions drawn from the data must be interpreted with caution. The study was not powered to detect differences in AFS or any other clinical outcome, it serves as a description of 'real world', consecutive patients presenting with CLTI secondary to IP disease at our unit. Clearly selection bias will have affected the results of the study. This was apparent given the high prevalence of comorbidity in the group of patients receiving PBA in comparison to those undergoing BS. What is unknown are the proportion of patients who would have been suitable and fit enough to be considered for both forms of re-vascularisation. Given that this data originates from a single, UK vascular centre, results may also not be generalisable to the other units in our country or internationally.

2.3.7 Conclusions

In conclusion, in CLTI patients selected for IP revascularisation at our unit, PBA was associated significantly poorer AFS and OS when compared to BS. This may be explained, at least in part, by the higher prevalence of diabetes and ischaemic heart disease in this group. However,

patients undergoing BS had high peri-procedural morbidity and increased length of stay. Overall, clinical outcomes in the current cohort were very similar to those reported in BASIL-1, although current patients undergoing BS fared somewhat better and those undergoing PBA fared somewhat worse. Current data support the BASIL-1 sub-group analysis and suggest that CLTI patients requiring revascularisation for IP disease should have BS where possible and that PBA should usually be reserved for patients who are not suitable for BS.

2.4 THE BASIL PROSPECTIVE COHORT STUDY

The BASIL prospective cohort study (PCS) ran alongside BASIL-2 at HEFT UHB between July 2014 and September 2016. All patients with CLTI admitted to this hospital in East Birmingham were screened for eligibility for the trial, outcomes from those not entered into the study were also recorded as well as detailed baseline demography. One criticism of the BASIL trial was the perceived lack of generalisability to the total CLTI population, one of the aims of this section were to determine the generalisability of the BASIL-2 study to total patient cohorts. Secondary aims were to document outcomes in 'all-comers' with CLTI and to explore, in particular, how patients with CLTI secondary to IP disease were managed.

2.4.1 Abstract

Introduction:

One criticism of the BASIL-1 trial was that results were obtained from a homogenous population that did not represent the heterogeneity that clinicians experienced in everyday clinical practice. To inform regarding generalisability for patients screened and randomised into BASIL-2, as well as to capture outcomes of all-comers with CLTI we prospectively studied consecutive patients admitted to a large, tertiary, academic vascular unit.

Methods:

Ethical approval was granted as part of the BASIL-2 trial for collection of baseline data for all patients with CLTI who presented to our unit. Patients were followed by screening routinely collected electronic data for the following outcome measures; amputation free survival, overall survival, limb salvage, freedom from re-intervention and major adverse limb events.

Results:

Data were gathered on 259 patients presenting with CLTI between 1st July 2014 to 30th September 2016. For those undergoing infrainguinal revascularisation the median time to treatment following emergency admission to hospital was 5 days. There was no significant difference in time to treatment between those undergoing endovascular treatment or bypass surgery (p=.3). Patients accounted for a total of 4,759 bed days in hospital on the primary admission. Overall survival for the whole cohort was estimated at 1 year (69.9%), three years (50.6%) and five years (32.9%). Those with IP disease who were considered to have a salvageable limb, a physiological reserve to withstand either open or endovascular revascularisation and adequate venous conduit 16/75 (21.3%) were randomised into the BASIL-2 Trial. For those undergoing an attempt at IP revascularisation there were no differences in AFS (HR 1.01, 95%CI: 0.61 – 1.70, Log-rank p=1.0), OS (HR 1.12, 95%CI: 0.64 – 1.95, Log-rank p=.6), FF-R (HR 0.83, 95%CI: 0.35 – 1.97, Log-rank p=.7), MALE (HR 1.12, 95%CI: 0.58 – 2.15, Log-rank p=.6) or LS (HR 0.93, 95%CI: 0.43 – 2.04, Log-rank p=0.9) out to five years.

Conclusions:

We have described real world outcomes in all comers presenting with CLTI, highlighting in a modern cohort the poor outcomes experienced in this challenging patient group of patients. Despite reported issues with generalisability, a reasonable proportion of eligible patients were enrolled into BASIL-2 during the data collection period.

2.4.1 Introduction

The evidence base underpinning the management of chronic limb threatening ischaemia (CLTI) is poor and generally of low quality. To date, the BASIL-1 trial[9] remains the only RCT to have compared clinical outcomes in patients undergoing plain balloon angioplasty (PBA) or surgical bypass for severe limb ischaemia (SLI) secondary to femoropopliteal (FP) +/- infrapopliteal (IP) disease. Currently, evidence gaps are being addressed in those patients with primarily IP+/- FP disease. The BASIL-2[12] trial, funded by the NIHR HTA (http://www.nets.nihr.ac.uk/projects/hta/123545) has recently completed randomisation of patients with IP+/- FP disease who are suitable for revascularisation to either vein bypass (VB) or best endovascular treatment (BET) and is due to report in 2022.

Patients with CLTI often present with heterogenous patterns of disease both clinically and anatomically and a "one size fits all" approach to managing such patients is often not possible or appropriate. Some criticise the BASIL-1 trial regarding generalisability of the findings given that each patient with CLTI is inherently different. This is further compounded by the fact that there was a high cross over rate (approximately 30%) in the trial with approximately 30% of patients randomised to VB who ended up receiving BET.

When considering intellectual equipoise between VB and BET in patients with CLTI secondary IP+/-FP disease, it is clear that the evidence base currently is severely lacking. Clinician bias, institutional factors and patient preferences have all been reported as potential barrier to recruitment in BASIL-2. In BASIL-1 some criticised the fact that around 29% of patients who presented to vascular services at the lead institution (formerly, The Heart of England

Foundation Trust, University Hospitals Birmingham) (HEFT UHB) were deemed eligible for the trial, 68% of which were actually randomised.

Data from a selected subgroup of patients from the BASIL-1 trial with CLTI secondary to infra-popliteal disease have been analysed separately[57]. In 104 patients undergoing either IP PBA or IP VB we demonstrated clinically important, but not significant differences in AFS (HR 0.68, 95% CI 0.42–1.10, p = .1) or OS (HR = 0.60, 95% CI 0.36–1.02, p = .06) favouring a VB first strategy. Patients who underwent VB also experienced significantly quicker and more sustained relief from ischaemic rest pain (p=.005) at the expense of a longer length of initial hospital stay (Median 18 days vs. 10 days, p<.0001) and increased thirty day morbidity ((RR 2.86, 95% CI 1.25–6.53, p = .01).

Some argue that such outcomes are outdated, particularly in reference to patients undergoing endovascular therapy. However, when comparing the BASIL-1 IP PBA data (1999-2004) with a cohort a decade later (2009-2013) we published data that demonstrated no improvements in crude outcomes such as AFS (HR 1.00, 95%CI: 0.65-1.54, P = 1.0), OS (HR = 1.04, 95% CI: 0.66-1.62, P = .9) or re-intervention (HR = 0.61, 95% CI: 0.29-1.27, P = .2) despite a significant improvement in immediate technical success from 73% to 90% (p=.01).

To give this more context in terms of comparison with more modern open surgery we compared IP VB and IP PBA in the same cohort (2009-2013) from HEFT UHB[110]. In this cohort AFS (HR 0.50, 95% CI:0.33 – 0.76, p=.001) and OS (HR 0.42, 95% CI:0.27 – 0.66, p<.001) were significantly better in those selected for IP VB again at the expense of higher thirty day morbidity (RR 3.75, 95% CI: 1.72 – 8.15, p<.001) and longer length of in-hospital stay during the index admission (Median 9 days vs. 5 days, p=.003).

On balance, if considered fit enough and venous conduit is available then patients with CLTI secondary to IP disease probably should have VB as the first revascularisation strategy.

Little is known or regarding the outcomes of CTLI patients who do not undergo an attempt at revascularisation but who receive primary amputation or who are managed conservatively. A review article in 2015 reported results from 13 studies in 1,527 patients with "untreated CLTI" which reported an all-cause mortality rate of 22% and a major amputation rate of 22% at 12-months. However, the authors concluded that the quality evidence was low due to "increased risk of bias and inconsistences"[71]. There are few studies published reporting detailed outcomes prospectively in this challenging patient group.

To address such gaps in the literature we aim to prospectively collect data for all CLTI patients screened for BASIL-2 at HEFT UHB to determine the following;

1. The proportion of patients presenting with CLTI eligible for BASIL-2
2. The proportion of patients eligible for BASIL-2 who were randomised
3. The outcomes of those patients undergoing infrainguinal revascularisation
4. The outcomes of those undergoing revascularisation for IP+/- FP disease
5. The outcomes of those CLTI patients who underwent primary amputation surgery or who were managed conservatively.

This study was collectively termed "The BASIL-Prospective Cohort Study (BASIL-PCS)".

2.4.2 Methods

All patients diagnosed with CLTI who presented to HEFT UHB between 1st July 2014 and the 30th September 2016 were approached for informed, written consent. Patients were provided with an information sheet regarding the BASIL-PCS and the BASIL-2 trial. Ethical approval was granted as part of the BASIL-2 trial (National Research Ethics Service, West Midlands,

UK (Coventry and Warwick) 3rd March 2014 (reference 14/WM/0057). Copies of the patient information sheet and consent form can be found in the appendices. In accordance with Good Clinical Practice (GCP) recommendations[111] patients were given 24 hours before consenting for entry into the BASIL-PCS. Patients included in BASIL-PCS consented to the collection of follow-up data by electronic means using local and national sources. Ethical cover did not extend to clinical follow up or the collection of health-related quality of life outcomes (HRQoL).

Eligible patients were approached for entry into BASIL-2 according to protocol[12] (see appendices). Entry into the BASIL-PCS did not influence the management or decision-making process of any patient, data collection was purely observational.

Patients who refused consent or who were considered ineligible followed their usual clinical pathway. Once consent was confirmed baseline metrics were recorded on specifically designed case report forms (CRFs), similar to those used in BASIL-2 (see appendices).

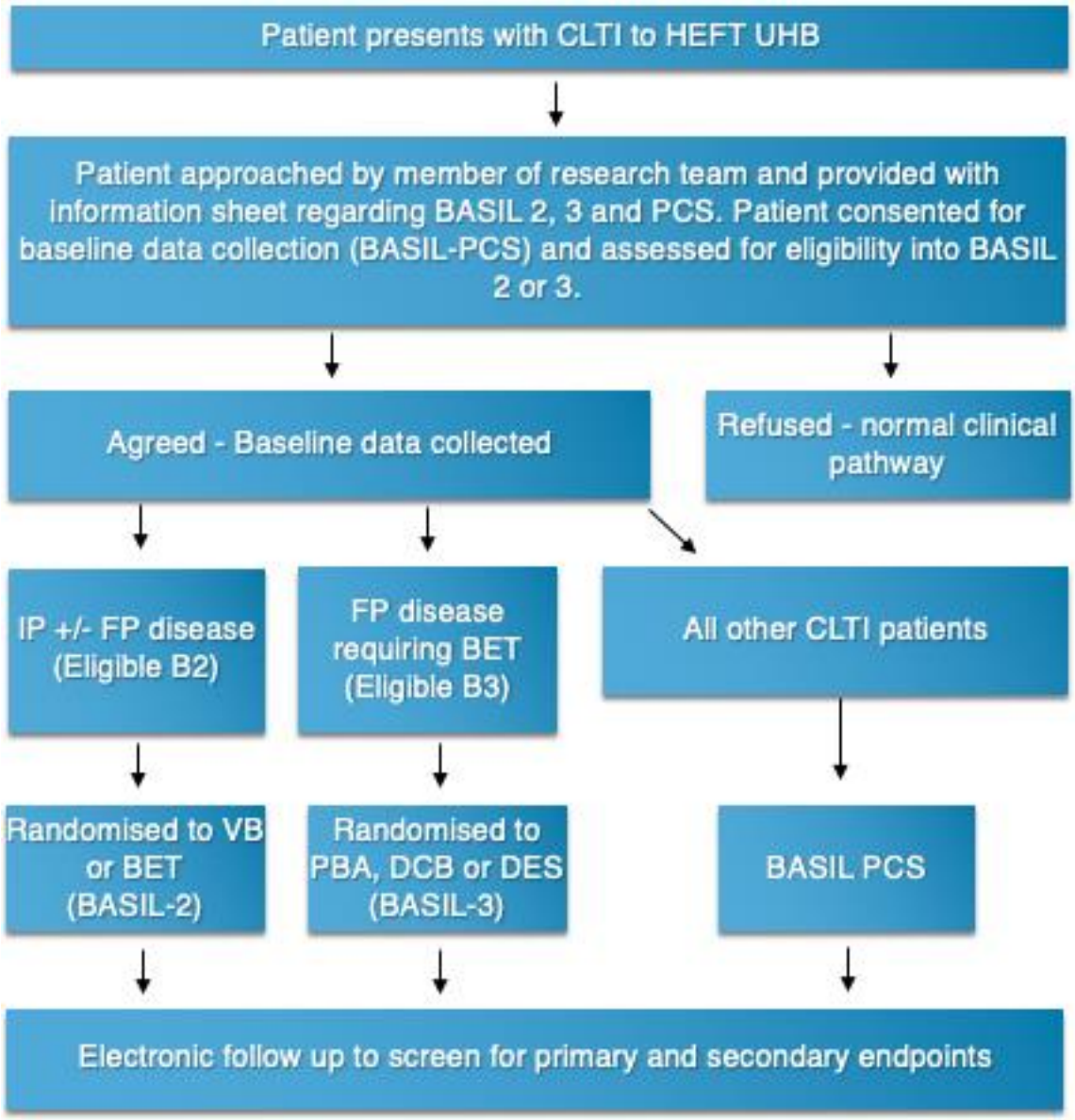
Figure 2.4.1. details the schema for recruitment into the BASIL-2, BASIL-3 trials and the BASIL-PCS.

All patients with CLTI were approached for informed consent by members of the BASIL-2 research team which comprised of two research fellows (MP, HD) and two research nurses (GB, LK). The majority of this was completed by the lead author (MP) except during times of annual leave or scheduled absence from HEFT UHB.

Consent for data collection only allowed electronic follow-up for patients not entered into BASIL-2 or BASIL-3. BASIL-2 follow-up CRFs were used to guide follow-up data collection for pre-defined endpoints by searching computerised hospital records collected as part of routine clinical practice (see appendices). Patients with CLTI often have multiple admissions

and access to secondary health care; to capture this activity and quantify its impact on health resource usage, electronic records were interrogated at regular intervals.

Figure 2.4.1 Schema for recruitment into BASIL-2, BASIL-3 and BASIL-PCS



Abbreviations: BASIL: Bypass versus Angioplasty in Severe Ischaemia of the leg, PCS: Prospective Cohort Study, FP: Femoropopliteal, IP: Infrapopliteal, BET: Best Endovascular Treatment.

N.B: All patients who presented to HEFT UHB with CLTI during the study period were included in the BASIL-PCS cohort (including those randomised into BASIL-2 and 3).

The BASIL-PCS was an integral part of the BASIL trials initiative at HEFT UHB as detailed screening and patient contact for all patients with CLTI identified potential candidates for both recruiting BASIL trials as well as providing much needed unit focus on this challenging patient group.

Ethical approval and subsequent consent provided the research team with the permission to store name, gender, date of birth, hospital and NHS numbers to allow "responsible individuals to track my future progress". A copy of the screening consent form, original ethical approval and patient information sheets can be found in the appendices.

Baseline demographics including; age, gender, past medical history, medications, previous vascular and endovascular interventions, haemodynamics (ABPI, TBPI (if incompressible vessels)), wound scores (Wound Ischaemia Foot Infection (WIfI[29]), Perfusion Extent Depth Infection Score (PEDIS[30])) and imaging modalities used to assist decision making regarding revascularisation. Global Anatomic Staging System (GLASS) scores were also calculated retrospectively by MP using available digital subtraction angiography (DSA) and computer-tomography angiography (CTA) imaging, using the methodology stated in the recently published Global Vascular Guidelines (GVG)[13,14]. The GLASS concept was not yet defined at the time of original data collection. Magnetic resonance angiography is not routinely used at HEFT UHB. GLASS has been validated using patients from the BASIL-1 trial[55].

Detailed information was also collected regarding the initial in-hospital management of the patients including; revascularisation a patient received (if applicable), immediate technical success of any intervention and modality of treatment, if any.

BASIL-2 Screening

The percentage of those patients receiving IP revascularisation (surgical bypass distal to the below knee popliteal artery and endovascular therapy including the tibio-peroneal trunk and beyond) was recorded as was the number of those patients randomised into BASIL-2 to provide information regarding generalisability of the study.

In-hospital outcomes

Short-term, in-hospital outcomes during the index BASIL-PCS admission were recorded for those undergoing infrainguinal revascularisation including; time to revascularisation from presentation, length of hospital stay as well as inpatient mortality and morbidity. Re-admissions to hospital within thirty-days of discharge were also recorded.

Long term outcomes

All patients were screened electronically for endpoints at regular intervals following discharge until a censor date of the 7th December 2020. Patients enrolled into BASIL-2 or BASIL-3 were followed as per protocol for each trial[12,107] which also involved clinical, haemodynamic and HRQoL based data collection. Such patient's data was collected for the BASIL-PCS independently of the CRFs used for either trial (not including HRQoL data or other clinical-based follow-up). Overall survival and mortality were assessed for the whole cohort.

Infrainguinal Revascularisation + Infrapopliteal Subgroup analysis

Those undergoing infrainguinal revascularisation were assessed in more detail. Best endovascular treatment (BET) was compared with bypass surgery in terms of demographics, limb threat (GLASS, WIfI) as well as; amputation free survival (AFS), overall survival (OS), limb salvage (LS), freedom from arterial re-intervention in the index limb (FFR) and major

adverse limb events (MALE, defined as loss of patency, arterial re-intervention or amputation in the index limb). The censor date of the 7th December 2020 was used for subsequent analyses.

Those with infrapopliteal +/- femoropopliteal disease who received either BET or bypass were also analysed as a separate subgroup with the same long-term outcomes as the total cohort of patients receiving infrainguinal revascularisation.

Conservative treatment & Amputation

Those managed conservatively, or who undergo MLLA during index BASIL-PCS admission will also be analysed as separate subgroup in terms of limb threat (WIfI, GLASS), overall survival and mortality.

Financial burden on the National Health Service (NHS)

The financial impact on HEFT UHB will be estimated using the NHS reference costs 2017/18[112] by calculating the cost of primary BASIL-PCS and subsequent admissions to hospital until the previously specified censor date.

Statistical Analysis

Simple descriptive statistics were performed to describe the natural history of patients with CLTI in our cohort. The Shapiro-Wilk test was used to determine the distribution of data prior to analysis. Analysis was performed on an intention to treat basis. Differences in time to event outcomes, if any, will be assessed using the Kaplan-Meier method, expressed as a hazard ratio with 95% confidence intervals (CI). For each Kaplan Meier curve estimate once the number at risk reaches less than 20% of the total cohort results should be interpreted with caution as survival estimates are likely to become less reliable.

Other outcome measures were compared using standard methods (Fisher's Exact Test or Chi-squared for dichotomous outcomes, log-rank test for time to event data, Mann-Whitney U for continuous variables, Kruskal-Wallis for multiple group-based comparisons). All analysis was performed to a 95% confidence interval. Statistical analysis was performed using R version 3.6.1 (2019-07-05)© 2019. The R Foundation for Statistical Computing. Graphical illustrations presented were prepared using GraphPad Prism 9 software ver. 9.0.1, GraphPad Software, LLC©.

2.4.3 Results

Description of the entire cohort

Between 26th June 2014 and 30th September 2016, two hundred and fifty-nine (259) patients presented to HEFT UHB with CLTI. This accounted for 272 limbs as defined by the criteria set in BASIL-2[12]. Two patients were unable to provide informed consent due to terminal presentations associated with acute illness that prevented consenting due to a lack of capacity.

Following admission to hospital and presentation on the vascular specialist ward (or other depending on bed status), patients were assessed by the authors (MP, GB or HOBD) in terms of presenting history, demographics and a thorough clinical examination to assess wound status and haemodynamics. The demographics of the 259 patients captured are detailed in Table 2.1.4.

The cohort of patients in BASIL-PCS were comorbid with a high prevalence of diabetes (55.2%), many of which were dependent on insulin (29.3%). Around a third of patients were active smokers, with just under 80% of patients having some history of a smoking habit. It is unclear how many of these patients were offered smoking cessation support, and what form this came in, during their primary admission from the data collected. Pack year history was not recorded. All patients were asked in their own words to describe their ethnicity, results were

then tabulated. The majority of patients described their ethnicity as "White British" (89.6%). Most affected limbs had tissue loss (81.3%) and many reported experiencing ischaemic rest pain (66.5%).

The number of patients with ischaemic rest pain may appear lower than expected due to a reasonable proportion of patients (45/249, 18.1%) who had altered foot sensation secondary to neuropathy. The prescription of medication with the aim of reducing serum lipid levels was poorer than expected at 72.6% and overall, only 137 patients (62.5%) were taking "Best Medical Therapy" (BMT) on admission as stipulated by NICE[22].

Table 2.4.1 Baseline demographics of patients presenting as an emergency to HEFT-UHB who were enrolled into the BASIL-PCS cohort.

Measure	**Number n=259**
Male sex	165 (63.7%)
Age (median, IQR)	73.9 (65.7 – 82.7)
Medical History	
Chronic Kidney Disease (eGFR <60ml/min/kg)	81 (31.3%)
Dialysis dependence	13 (5.0%)
Stroke/TIA	39 (15.1%)
Myocardial Infarction	55 (21.2%)
Angina	51 (19.7%)
Coronary Artery Bypass Grafting	31 (12.0%)
Percutaneous Coronary Intervention	25 (9.7%)
Diabetes	143 (55.2%)
Insulin dependence	76 (29.3%)
Smoking Status	
Current	77 (29.7%)

Ex	124 (47.9%)
Never	58 (22.4%)
Obesity (Body Mass Index >30)	33 (12.7%)
Mobility	
Independent	75 (29.0%)
Walks with aid	146 (56.4%)
Wheelchair bound	31 (12.0%)
Bed bound	5 (1.9%)
Unavailable	2 (0.8%)
Ethnicity	
White British	232 (89.6%)
White Irish	8 (3.1%)
Chinese	1 (0.4%)
Black African	1 (0.4%)
Black Caribbean	8 (3.1%)
Asian Pakistani	6 (2.3%)
Asian Indian	1 (0.4%)
Kashmiri	1 (0.4%)
Other	1 (0.4%)
Clinical Status	
Unilateral disease	246 (95%)
Bilateral disease	13 (5%)
Limbs n= 272	
Rest pain	181 (66.5%)
Tissue loss	221 (81.3%)
Both	129 (47.4%)

Distribution of tissue loss	Wounds (n=262)
Hallux	76 (29.0%)
Other toes	66 (25.2%)
Forefoot	44 (16.8%)
Ankle	23 (8.8%)
Above ankle	53 (20.2%)
Medical Therapy	
Aspirin	142 (45.2%)
Clopidogrel	64 (24.7%)
Other antiplatelet agent	6 (2.3%)
Cholesterol reducing agent	188 (72.6%)
Anti-hypertensive agent	191 (73.7%)
Warfarin	27 (10.4%)
Direct Oral Anticoagulant	7 (2.7%)
*Considered "Best Medical Therapy"**	162 (62.5%)

*Abbreviations: eGFR – Estimated Glomerular Filtration Rate, TIA- Transient Ischaemic attack. *Best Medical Therapy as according to NICE Clinical Guideline 147*[22].

BMT in the UK consists of an antiplatelet agent (aspirin 75mg, clopidogrel 75mg or similar once daily) plus a lipid modifier (statins, fibrates etc). If patients were already taking an anticoagulant (coumarins, direct oral anticoagulants) and a lipid modifier, but not an antiplatelet this was identified as an acceptable form of BMT also.

In terms of clinical assessment, a high proportion of patients underwent; Ankle brachial pressure index measurement (ABPI, 216 patients, 83.4%), Perfusion Extent Depth Infection Sensation score (PEDIS, 249 patients, 96.2%) and Wound Ischaemia Foot infection staging (WIfI, 225 patients, 86.9%). Table 2.4.2 summarises the clinical assessments performed as part of BASIL-PCS.

In those patients who had wounds (196/249, 78.7%) that were assessed by PEDIS, an extremely high proportion had a PEDIS score of 7 or more, (154/196, 78.5%) which signifies serious limb threat. In terms of WIfI staging, well over half of those assessed (142/225, 63.1%) were found to be at clinical stage 3 (69/225, moderate risk of amputation, very low potential benefit of revascularisation) or stage 4 (73/225, high amputation risk, very low potential benefit of revascularisation) in the most symptomatic limb at presentation.

The most common form of definitive imaging used to confirm the TAP in patients presenting was CT angiography (97 patients, 42.1%). This was also the most common first line imaging (126 patients, 48.6%). A proportion of patients (21, 8.1%) were not imaged due to either; overwhelming tissue loss, severe medical comorbidity or palliative presentation states that rendered imaging inappropriate and not in the best interests of the patient. Table 2.4.4 details the imaging modalities used in BASIL-PCS.

In terms of previous interventions, 51 (19.7%) patients had undergone previous endovascular revascularisation and 37 (14.3%) had undergone surgical revascularisation. Most importantly 24 (9.3%) patients had undergone an attempt at revascularisation within the 12-months preceding hospital admission and entry into BASIL-PCS. Table 2.4.3 details previous interventions. Forty-one patients (18.4%) had already undergone digital amputation to toes on either foot and 24 (9.3%) had already had the contralateral limb amputated above the ankle secondary to diabetic complications or CLTI.

Table 2.4.2 A summary of the clinical assessments performed in patients presenting to HEFT-UHB with CLTI and entered into the BASIL-PCS.

Ankle Brachial Pressure Index	
Symptomatic leg	
Not done	43 (16.6%)
Recorded	216 (83.4%)
Incompressible	29 (11.2%)
Unrecordable (no foot signal)	64 (24.7%)
Median ABPI (IQR)	0.53 (IQR 0.4 – 0.72)
PEDIS	
Completion rate	249 (96.2%)
Perfusion status n=249	
Grade 1: no symptoms of PAD	0 (-)
Grade 2: Symptoms or signs of PAD but no CLTI	0 (-)
Grade 3: CLTI	249 (100%)
Extent of tissue loss n=249	
No wound	53 (21.3%)
Less than 1cm^2	22 (8.8%)
Between 1-3cm^2	34 (13.6%)
More than 3cm^2	141 (56.6%)
Depth of tissue loss n=249	
No wound	53 (21.3%)
Grade 1: Superficial Full thickness Ulcer	51 (20.5%)
Grade 2: Ulcer penetrating below dermis to skin structures	93 (37.3%)
Grade 3: All subsequent layers of foot including bone/joint	52 (20.9%)
Infection n=249	
Grade 0: no symptoms and signs	117 (47.0%)

Grade 1: Inflammation of skin/subcutaneous tissues only	70 (28.1%)
Grade 2: Extensive erythema deeper than skin	42 (16.9%)
Grade 3: Systemic Inflammatory Response syndrome (SIRS)	20 (8.0%)
Sensation n=249	
Grade 0: No loss of protective sensation	204 (81.9%)
Grade 1: Loss of protective sensation	45 (18.1%)
Median Total Score of those with wounds (IQR)	8 (IQR 8 – 9)
PEDIS ≥7 in those with wounds	154 (60.6%)
Wound Ischaemia Foot infection scores (WIfI)	
WIfI completion	225/259 (86.9%)
Wound status n=225	
Grade 0: Ischaemic rest pain only	44 (19.6%)
Grade 1: Minor tissue loss	68 (30.2%)
Grade 2: Major tissue loss	55 (24.4%)
Grade 3: Extensive Ulcer/Gangrene	58 (25.8%)
Ischaemic status n=225	
Grade 0: ABPI >0.8, ASP >100 (mmHg), TP TcpO2 >60 (mmHg)	64 (28.4%)
Grade 1: ABPI 0.6-0.79, ASP 70-99, TP TcpO2 40-59)	33 (14.7%)
Grade 2: ABPI 0.4-0.59, ASP 50-69, TP TcpO2 30-39	35 (15.5%)
Grade 3: ABPI <0.4, ASP <50, TP TcpO2 <30	93 (41.3%)
Foot infection n=225	
Grade 0: Wound without infection	111 (49.8%)
Grade 1: >2 manifestations of infection, cellulitis	59 (26.2%)
Grade 2: Cellulitis extending >2cm from wound	33 (14.7%)
Grade 3: Infection in a patient with systemic or metabolic toxicity	22 (9.8%)
Total WIfI clinical grade (perceived risk of limb loss) n=225	
Grade 1: Very Low	24 (10.7%)

Grade 2: Low	59 (26.2%)
Grade 3: Moderate	69 (30.7%)
Grade 4: High	73 (32.4%)

All but 26 (11.6%) patients had imaging available to determine a definitive clinical GLASS stage. These patients either went straight to primary amputation due to extensive tissue destruction or sepsis or only underwent duplex ultrasonography prior to open revascularisation or conservative treatment. Supra-inguinal, infra-inguinal and overall GLASS scores were allocated to each patient based on DSA or CTA imaging.

Most patients (145/233, 62.2%) had DSA imaging available to review, the remaining patients had various other imaging modalities that were used to derive GLASS stage (carbon dioxide angiogram 3/233 1.3%, CT 82/233 35.2%). Following review of these images a further eleven patients had imaging that was inadequate to delineate a final stage, leaving 222 (85.7%) for final GLASS analysis. One hundred and ninety-one patients had adequate foot view imaging to calculate a pedal modifier.

The majority of patients were allocated GLASS stage III (68.9%) which signifies high complexity disease with an expected immediate endovascular treatment failure of more than 20% or limb based patency of less than 50% at 1-year[13,14]. Table 2.4.5 demonstrates the frequency of GLASS scores.

Table 2.4.3 Previous vascular interventions in patients entered into the BASIL-PCS, separated by modality, limb and time.

Ipsilateral Limb		**<12months**	**>12 months**
Endovascular	Suprainguinal	3 (1.2%)	2 (0.8%)
	Infrainguinal	14 (5.4%)	16 (6.2%)
Surgical	Suprainguinal	1 (0.4%)	5 (1.9%)
	CFA endarterectomy only	1 (0.4%)	0 (-)
	Infrainguinal bypass	5 (1.9%)	9 (3.5%)
Contralateral Limb			
Endovascular	Suprainguinal	1 (0.4%)	2 (0.8%)
	Infrainguinal	1 (0.4%)	12 (4.6%)
Surgical	Suprainguinal	0 (-)	4 (1.5%)
	CFA endarterectomy only	1 (0.4%)	1 (0.4%)
	Infrainguinal bypass	1 (0.4%)	9 (3.5%)
Amputation	Minor Amputations	65 (25.1%)	
	Above Knee Amputation	6 (2.3%)	
	Below Knee Amputation	18 (6.9%)	
Total	Patients with previous Endo Revascularisation	51 (19.7%)	
	Patients with previous surgical revascularisation	37 (14.3%)	

Table 2.4.4 Imaging modalities used in patients presenting to HEFT-UHB with CLTI in the BASIL-PCS and the frequency of which they were used during the patient's primary admission.

Imaging modality	**n=259**
Primary	
No imaging performed	21 (8.1%)
Duplex Ultrasound	56 (21.6%)
Magnetic Resonance Angiography	0 (-)
Computed Tomography Angiography	126 (48.6%)
Digital Subtraction Angiography	56 (21.6%)
Definitive imaging	
No imaging performed	21 (8.1%)
Duplex Ultrasound	32 (12.4%)
Magnetic Resonance Angiography	0 (-)
Computed Tomography Angiography	109 (42.1%)
Digital Subtraction Angiography	97 (37.4%)
Number of different imaging modalities used per patient	
0	21 (8.1%)
1	168 (64.9%)
2	62 (23.9%)
3	8 (3.1%)

Table 2.4.5 Global Anatomic Staging System scores for patients presenting to HEFT UHB with chronic limb threatening ischaemia.

Suprainguinal Disease	**n=233**
0A	155 (66.5%)
0B	14 (6.0%)
1A	13 (5.6%)
1B	16 (6.9%)
2A	15 (6.4%)
2B	20 (8.6%)
Infrainguinal GLASS stage	*n=222*
GLASS stage 1	22 (9.9%)
GLASS stage 2	47 (21.2%)
GLASS stage 3	153 (68.9%)
Severe calcification	41 (18.5%)
Pedal modifier (219 patients with adequate imaging to determine foot view)	*n=219*
P0	48 (21.9%)
P1	98 (44.7%)
P2	72 (32.9%)

*GLASS tables explaining the various gradings and stages can be found in the appendices.

Patient Management

Of the total cohort, 175 patients (67.6%) underwent an attempt at revascularisation during the index admission. Figure 2.4.2 and 2.4.3 demonstrate how patients were managed by the admitting physician in terms of a “first treatment strategy” following emergency presentation.

Figure 2.4.2 Pie chart demonstrating overall management strategies for patients presenting to HEFT UHB with CLTI

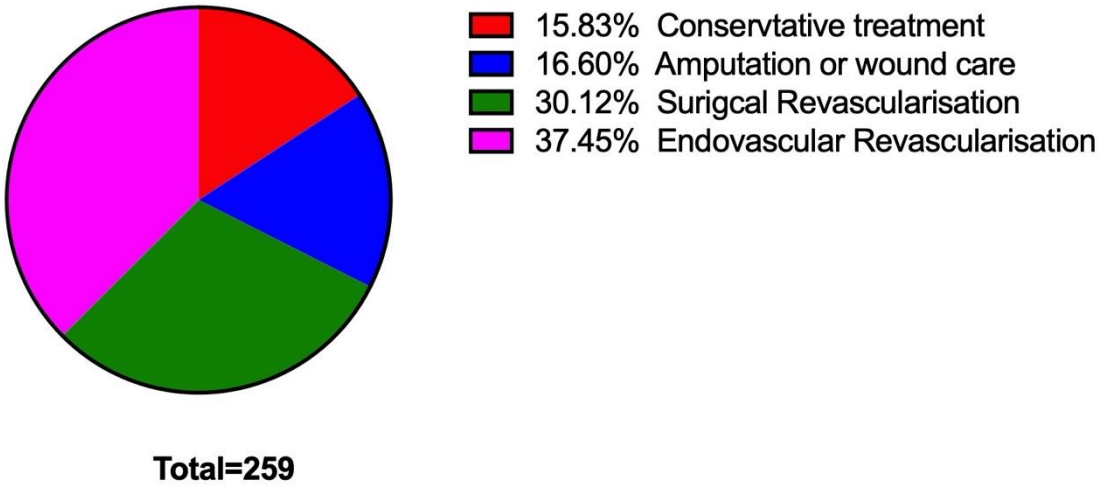
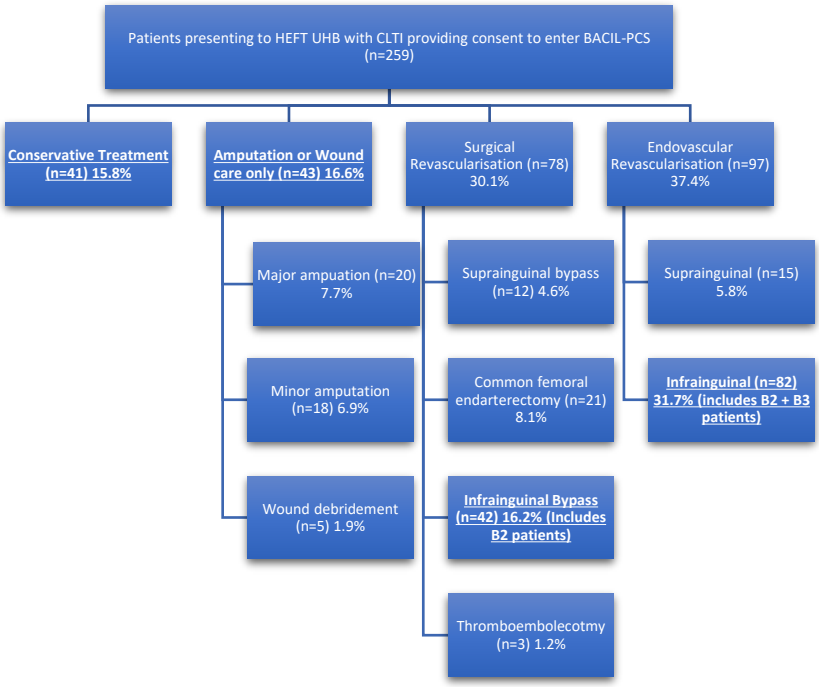


Figure 2.4.3 Flow diagram to represent how patients were managed as a first treatment strategy when presenting to HEFT UHB with chronic limb threatening ischaemia.

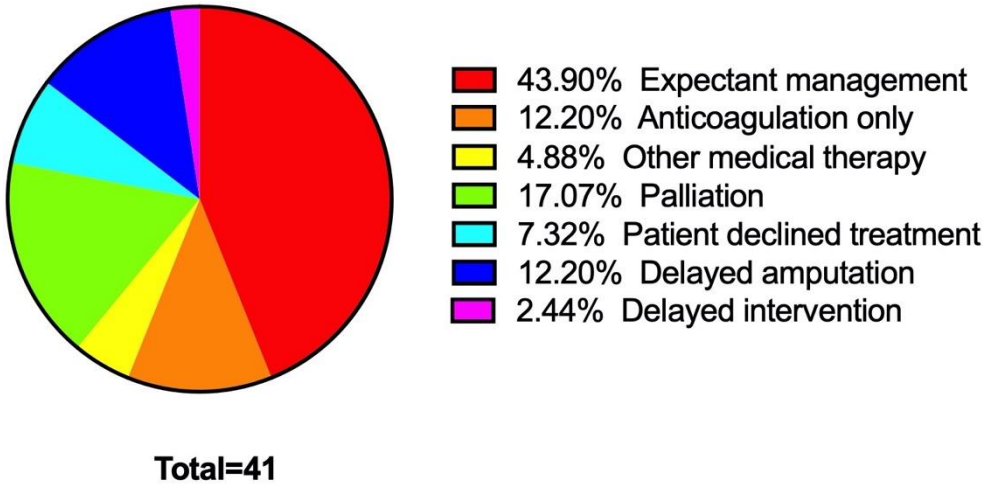


N.B. Groups underlined are of specific interest in this thesis.

Conservative Treatment

Conservative treatment was defined as any patient who did not undergo an attempt at revascularisation, amputation or any active intervention other than medication, palliation or expectant therapy on the index admission (summarised in Figure 2.4.4). Eighteen patients (43.9%) were managed expectantly, meaning that they did not have any suitable options for revascularisation, they were too unfit to contemplate revascularisation or amputation but not unwell enough to be considered palliative during the index admission. Such patients were discharged home with wound care (if applicable), analgesia and best medical therapy. None of these 18 patients returned for further intervention. Seven patients (17.1%) were treated with medication only, including five patients who were anticoagulated for acute on chronic thrombosis in situ with no option for revascularisation and two with antibiotics and anticoagulation for infected, occluded previous prosthetic bypass grafts (one femoro-above knee popliteal, one axillo-bifemoral). A further seven patients (17.1%) were palliated directly as a result of their symptoms during the index admission. All of which died in hospital on, or shortly after discharge. A small proportion of patients underwent amputation (5/41, 12.2%, four major, above ankle and one minor, digital) during a later admission having been deemed unsuitable for revascularisation but not yet severe enough symptomatically to require amputation. Three patients were offered treatment (two infrainguinal endovascular treatment, one infrainguinal bypass surgery) but declined and were not seen again by our vascular services. One remaining patient underwent delayed endovascular treatment on another admission (1/41, 2.4%). WIfI stages were spread fairly equally in the group (WIfI stage I 3/41, 7.3%, WIfI stage 2 12/41, 29.3%, WIfI stage 3 11/41, 26.8%, WIfI stage 4 12/41, 29.3%). WIfI stage could not be calculated in three patients due to missing haemodynamic indices.

Figure 2.4.4 Pie chart demonstrating how patients were treated conservatively in the BASIL-PCS



Amputation & wound care

Patients undergoing some form of amputation or wound care at index admission during the BASIL-PCS recruitment period accounted for 43 presentations (16.6%). Patients in this category had not had an attempt at revascularisation during this "index BASIL-PCS" admission. Five patients (5/43, 1.9%) only underwent wound care in the form of surgical debridement in an operating theatre, without attempt at revascularisation.

For the majority of patients undergoing minor amputation, 75% (15/20) had undergone previous vascular intervention prior to BASIL-PCS index admission. Two had previous ipsilateral, infrainguinal endovascular revascularisation attempts. Seven had already had other digits on the same foot amputated. In terms of contralateral disease, an additional two had previous infrainguinal endovascular treatment, one patient had a femoropopliteal bypass, five had digits removed from the opposite foot and one had undergone contralateral MLLA.

Surprisingly, the majority of patients undergoing MLLA during index BASIL-PCS admission were not prior known to our vascular service (11/20, 55%). Two had previously had an attempt at infrainguinal endovascular intervention in the ipsilateral limb, two had also had previous ipsilateral infrainguinal bypass surgery. One patient had a previous digital amputation. In terms of the contralateral limb, five underwent previous revascularisation attempts (three endovascular, two bypass). Four patients had already lost the contralateral limb. Patients in this subgroup had high limb threat in terms of WIfI stage (WIfI stage 4 7/20, 35%; WIfI stage 3 5/20, 35%; WIfI stage 2 3/20, 15%). Five patients did not have WIfI staging available as they underwent MLLA as an emergency out of hours and patients were entered into the study following surgery.

Surgical Revascularisation

The 78 patients undergoing an attempt at surgical revascularisation were further sub-divided into three distinct groups. Those undergoing suprainguinal or infra-inguinal treatments and those who only had an isolated common femoral endarterectomy.

Suprainguinal Surgical Revascularisation

Of the twelve patients who underwent suprainguinal revascularisation all were completed using prosthetic graft material. Four patients had unilateral, aorto-iliac/femoral bypass surgery +/- common femoral endarterectomy if required. Five underwent aorto-bifemoral bypass +/- common femoral endarterectomy and another three had a femoro-femoro crossover graft (one as an emergency for acute on chronic thrombosis in situ). All of which were immediately technically successful. However, one patient who underwent aorto-bifemoral bypass unfortunately died five days post-operatively from gut ischaemia. This patient underwent relook laparotomy which was open and close due to extensive intestinal infarction.

Common Femoral Endarterectomy

Twenty-one patients had a common femoral endarterectomy without any other revascularisation procedure. These were all completed via vertical groin incision. Most arteriotomies were repaired with Dacron© patch (18/20), two were closed primarily with vein. All were immediately successful from a technical perspective. Two patients who had arteriotomies closed with Dacron© that re-presented with patch infection, requiring surgical revision with vein patch.

Infrainguinal Surgical Revascularisation

In total 45 patients underwent infrainguinal surgical revascularisation at first presentation. 3 patients were treated as an emergency with thrombo-embolectomy for acute on chronic symptoms. This involved common femoral endarterectomy of the affected limb with distal embolectomy using sequential Fogarty catheters. The remaining 42 underwent surgical bypass. Technical information regarding one patient was unavailable due to missing theatre records. Technical details regarding conduit, anastomotic sites and technical failure can be found in Table 2.4.6.

The majority of patients had severe angiographical disease with 37/42 (88.1%) classified at GLASS stage 3. In one case there was insufficient imaging to obtain a GLASS stage. Run off into the pedal arches was variable (P0 - both arches intact 15/42, 35.7%; P1 – Single arch intact 13/42, 30.9%; P2 – no intact arch 11/42, 26.2%).

Table 2.4.6 Technical details of infrainguinal bypass surgery performed in the BASIL-PCS.

		Number n=41
Conduit	Reversed vein (when vein used alone)	12 (29.3%)
	Non-reversed vein (when vein used alone)	21 (51.2%)
	Leg vein	31 (75.6%) Ipsilateral GSV 2 (4.9%) contralateral GSV
		1 (2.4%) Bilateral SSV
	Arm vein	2 (4.9%)
	Prosthetic	3 (7.3%)
	Composite Sequential	3 (7.3%)
	No bypass performed as distal target not patent	1 (2.4%)
Proximal anastomosis	Common femoral artery	28 (70.0%)
n=40 as 1 abandoned	Superficial femoral artery	8 (20.0%)
	Profunda femoris artery	1 (2.5%)
	Above knee popliteal artery	0 (-)
	Below knee popliteal artery	3 (7.5%)
Distal anastomosis	Above Knee popliteal artery	4 (9.7%)
n=40 as 1 abandoned	Below Knee popliteal artery	10 (25.0%)
	Tibioperoneal trunk	3 (7.5%)
	Posterior tibial artery 1/3	5 (12.5%)
	Posterior tibial artery 2/3	4 (10.0%)
	Posterior tibial artery 3/3	3 (7.5%)
	Peroneal artery 1/3	2 (5.0%)
	Peroneal artery 2/3	0 (-)
	Peroneal artery 3/3	1 (2.5%)
	Anterior tibial artery 1/3	3 (7.5%)
	Anterior tibial artery 2/3	4 (10.0%)
	Anterior tibial artery 3/3	1 (2.5%)
	Dorsalis pedis	0 (-)
Technical failures	Early failure (<30 days)	2 (4.9%)

	Abandoned, no outflow vessel	1 (2.4%)
	Total technical failure	**3/41 (7.3%)**

Three patients had inadequate foot views to determine pedal runoff. Similarly, WIfI clinical stages were variable in this subgroup (Stage I 2/42, 4.1%; Stage II 10/42, 23.8%; Stage III 13/42, 30.9%; Stage IV 9/42, 21.4%).

It was not possible to calculate WIfI stage in 8 cases due to incomplete data (missing haemodynamic measures).

Seven patients underwent concurrent minor amputation in the same sitting. Two patients had concurrent inflow reconstruction (one iliac stent graft, one common femoral artery reconstruction).

Early technical failure was 7.3%. In one case the bypass was abandoned (CFA to AT3) as the LSV was found to be too friable following dissection for use. It was deemed inappropriate to use prosthetic material and the patient went on to have a below knee amputation. Another case (BKPA to PT3) was also abandoned due to lack of a patent distal target vessel. The patient unfortunately died as an inpatient due to congestive cardiac failure eight days from admission. The final patient's vein graft thrombosed (CFA to Peroneal 1/3) within twenty-four hours and they had an above knee amputation during the same admission ten days later.

Endovascular Revascularisation

The majority of patients (98/259, 37.8%) presenting to HEFT UHB with CLTI underwent endovascular treatment as a 'first' revascularisation strategy. Such patients were further

subdivided into suprainguinal revascularisation (without distal treatment) and infrainguinal revascularisation.

Suprainguinal Endovascular Revascularisation

All fifteen suprainguinal endovascular reconstructions were technically successful immediately following treatment confirmed by imaging. Five cases were bilateral. Two were combined with common femoral endarterectomy in a hybrid setting. Most were for stenotic (11/15, 73.3%) as opposed to occlusive disease. Eleven segments in the common iliac artery were treated as well as nine in the external iliac artery. Most patients were treated with plain balloon angioplasty only (10/15, 66.7%), three bare metal stents and 7 iliac stent grafts (Cook GORE® Viabahn® or Macquet® V12®) were also used.

Infrainguinal Endovascular Revascularisation

Patients who underwent infrainguinal endovascular treatment had GLASS stages estimated using angiographic imaging. The authors (MP and LM) were blinded to the outcomes of the patients analysed. All patients were given an inflow, femoropopliteal and infrapopliteal grades. Pedal and calcification modifiers were also used to estimate a final GLASS clinical grade which serves to predict immediate endovascular treatment failure as well as likelihood of limb-based patency (LBP) at 12-months. The process as outlined in the GVG was followed[14]. GLASS clinical stages could not be completed in two patients due to insufficient imaging, both patients had their procedures abandoned shortly after puncture due to intolerance. Detailed information regarding GLASS staging for these patients is presented in Table 2.4.7. The TAP is also presented in Table 2.4.7, this was determined by the least diseased tibial vessel.

Table 2.4.7 Infrainguinal GLASS scoring in those undergoing endovascular treatment in the BASIL-PCS study.

Concurrent Suprainguinal Disease	**n=81**
0A	79 (97.5%)
0B	0 (-)
1A	1 (1.2%)
1B	1 (1.2%)
2A	0 (-)
2B	0 (-)
Femoropopliteal (FP) GLASS stage	*n=80*
No FP disease	5 (6.3%)
FP stage 1	8 (10.0%)
FP stage 2	9 (11.3%)
FP stage 3	14 (17.5%)
FP stage 4	43 (53.8%)
Infrapopliteal (FP) GLASS stage	n=80
No IP disease	32 (40.0%)
IP stage 1	3 (3.8%)
IP stage 2	20 (25.0%)
IP stage 3	14 (17.5%)
IP stage 4	12 (15.0%)
Overall GLASS Clinical Stage	n=80
Grade 1	5 (6.3%)
Grade 2	22 (27.5%)
Grade 3	53 (66.3%)
Severe calcification	10/80 (12.5%)

Pedal modifier (78 patients with adequate imaging to determine foot view)	*n=77*
P0	6 (7.8%)
P1	43 (55.8%)
P2	28 (35.0%)
Target Artery Pathway	n=81
Anterior Tibial Artery	40 (49.4%)
Posterior Tibial Artery	14 (18.5%)
Peroneal Artery	26 (32.1%)

Table 2.4.8 details technical details of those who underwent infrainguinal endovascular treatment at first presentation during the BASIL-PCS recruitment period. WIfI stage calculation could not be completed in 8 patients due to missing haemodynamic data. More than 50% of patients had high limb threat in terms of WIfI stage (Stage I 11/74, 14.9%; Stage II 19/74, 25.7%; Stage III 22/74, 29.7%; Stage IV 23/74, 31.1%).

Technical data was missing in one patient, four patients did not have any imaging past the arterial puncture as the procedure was cancelled due to an inability to lie flat due to breathlessness or pain. These procedures were abandoned. Seventy-six patients were therefore available for analysis, accounting for 122 arterial segments.

Table 2.4.8 Technical details of those undergoing infrainguinal endovascular treatment in BASIL-PCS.

Vessels treated	**Named vessels**	**Frequency n=122**
Arteries treated	Proximal Superficial Femoral	21 (17.2%)
	Distal Superficial Femoral	30 (24.6%)
	Above Knee Popliteal	26 (21.3%)
	Below Knee Popliteal	17 (13.9%)
	Tibio-peroneal Trunk (TPT)	3 (2.5%)
	Posterior Tibial	3 (2.5%)
	Peroneal	7 (5.7%)
	Anterior Tibial	14 (11.5%)
	Dorsalis Pedis	0 (-)
Number of IP vessels treated	TPT most distal target	3 (2.5%)
	1 vessel	21 (17.2%)
	2 vessels	0 (-)
	3 vessels	0 (-)
Type of disease treated	Occlusive	60 (49.2%)
	Stenotic	62 (50.8%)
PBA and stent use	PBA only	94 (77.0%)
	PBA + Bail out BMS	5 (4.1%)
	DCB	13 (10.7%)
	DES	9 (7.4%)
Technical Failure	Inability to cross lesion	9/81 (11.1%)
	Residual stenosis	2/81 (2.7%)
	Embolism	1/81 (1.2%)
	Abandoned at patient request	4/81 (4.9%)
	Total technical failure	13/81 (16.0%)

BASIL-2 and BASIL-3

During the total period of study 16 and 19 patients were randomised into the BASIL-2[12] and BASIL-3[107] trials respectively. Data for these patients have been included in this analysis however individual outcomes from trial patients have not been assessed.

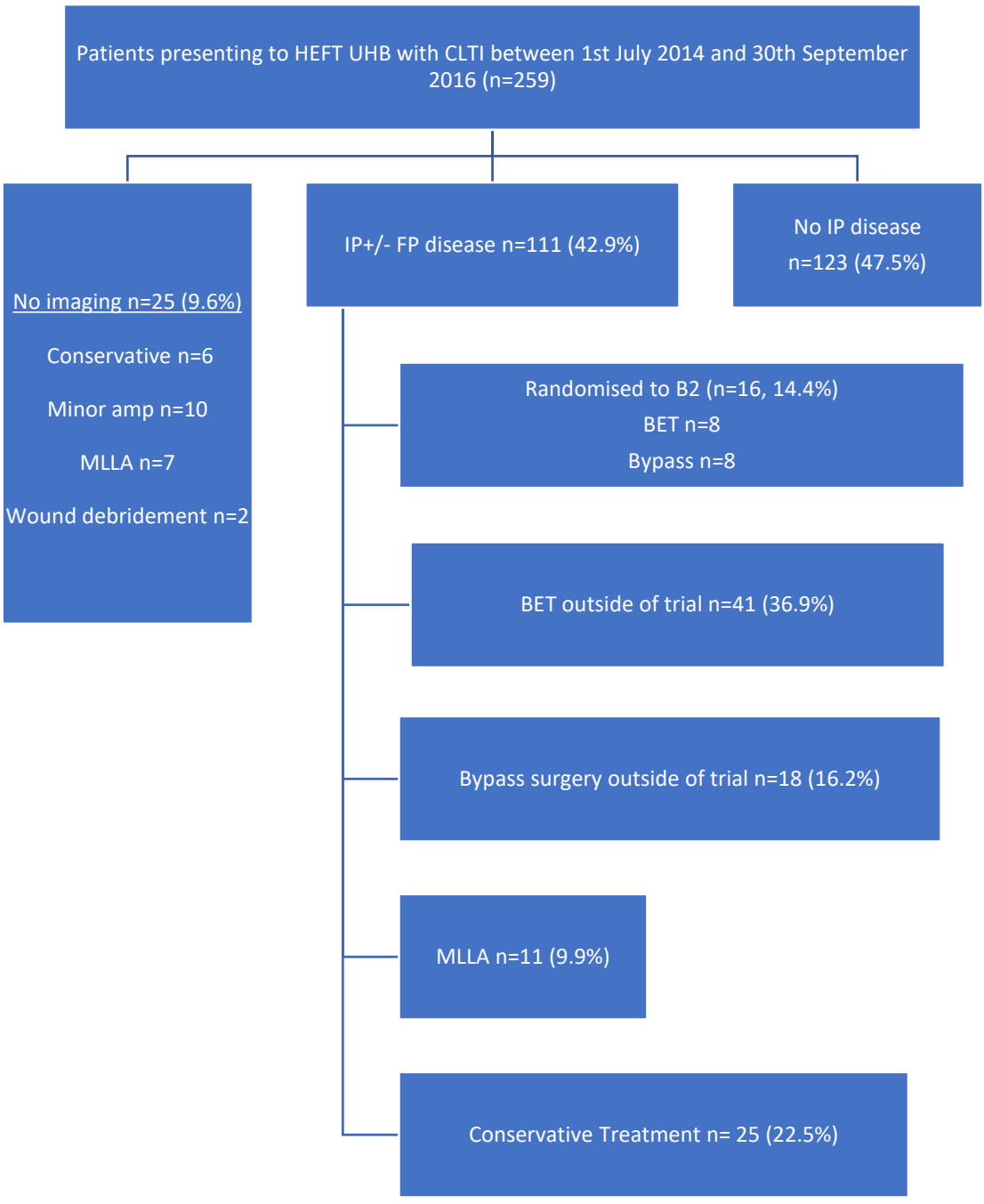
BASIL-2 recruitment commenced on the 1st July 2014. From the available cohort of total patients presenting to HEFT UHB with CLTI only a small proportion (16/259, 6.2%) were randomised either best endovascular treatment or vein bypass for IP+/-FP disease. Figure 2.4.5 represents screening and trial flow for the BASIL-2 trial at HEFT UHB.

A small proportion of patients (25/259, 9.6%) did not have imaging to define whether or not they had infrapopliteal disease prior to treatment. None of these patients were revascularised. All had a combination of wound care, amputation of some description or were treated conservatively due to their comorbidity or lack of options for revascularisation.

Although only a relatively small number of patients entered BASIL-2 from the total cohort, the proportion of those that were entered from those who could have been considered eligible was far greater. From those with IP disease and who were considered "fit" enough to receive an attempt at revascularisation 16/75 (21.3%) were randomised.

The BASIL-3 trial started recruitment in November 2015, over a year following the commencement of the BASIL-PCS. From November 2015 to September 2016 nineteen patients were randomised to plain balloon angioplasty +/- BMS, drug coated balloon +/- BMS or primary drug eluting stent in those with FP +/- IP disease who were considered for endovascular revascularisation. BASIL-3 focuses primarily on those with FP disease and therefore will not be discussed in further detail in relation to the BASIL-PCS in this Thesis.

Figure 2.4.5 Patient flow into the BASIL-2 trial during the BASIL-PCS at HEFT UHB.



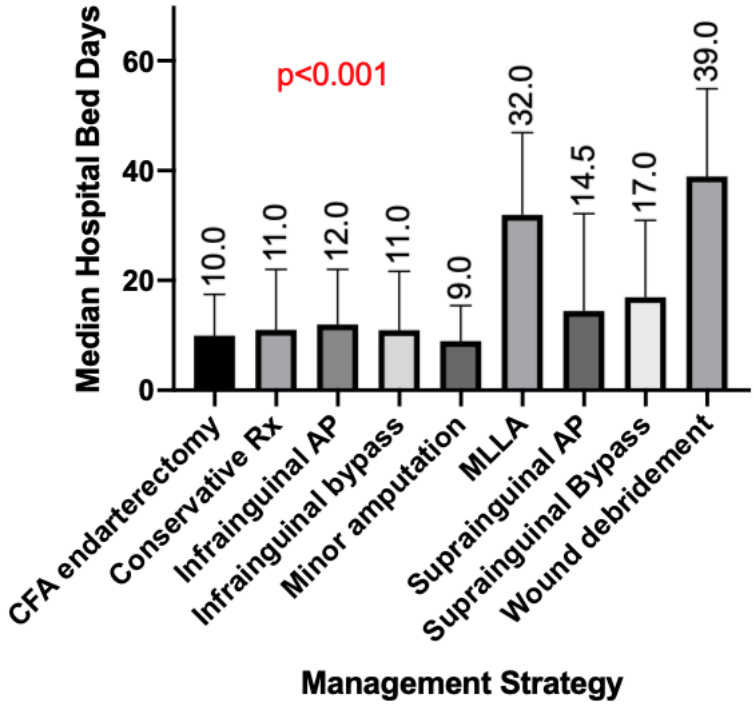
Time to revascularisation

Much has been made recently regarding the timing of revascularisation following admission to hospital with a diagnosis of CLTI. The Vascular Society of Great Britain & Ireland (VSGBI) has produced guidance regarding subtypes of patients that should be managed as an in-patient or out-patient. For inpatients a standard of revascularisation within 5-days of admission is mandated[113]. For those undergoing infrainguinal revascularisation the median time to treatment following emergency admission to hospital was 5 days (IQR 1 – 9). There was no significant difference in time to treatment between those undergoing endovascular treatment or bypass surgery (endovascular treatment 6 days, IQR 1.8 – 9.3 vs. bypass surgery 4 days, IQR 1.0 – 8.5, Mann-Whitney U, p=0.3).

Inpatient length of hospital stay

Patients in the BASIL-PCS accounted for a total of 4,759 bed days in hospital on the primary admission (4,605 ward days, 138 high dependency unit (HDU) bed days and 16 intensive care unit (ITU) bed days). The median length of stay per patient was 12 days (IQR 7-23 days). The majority of patients were discharged to their own homes (215/259, 83.0%), with a small proportion discharged to nursing or residential home care (23/259, 8.9%). A further 14 patients (5.4%) died in hospital during the primary admission. Seven patients were recruited in a semi-elective setting and were treated at a later date. Figure 2.4.6 demonstrates the median length of stay for the different subgroups of patients.

Figure 2.4.6 . Median Length of stay in different subgroups of patients in the BASIL PCS.



Interestingly, there was no significant difference in median total days spent in hospital for those patients undergoing either infrainguinal endovascular or surgical treatment (Infra-popliteal BET 12 days vs. Infra-popliteal BS 11 days, Mann-Whitney U, p=0.23).

Inpatient Mortality & Morbidity

Mortality during the index admission was 14/259 (5.4%). One patient died of sepsis following a failed common femoral endarterectomy and thrombo-embolectomy for acute on chronic symptoms 49 days following admission. Six patients were managed conservatively due to comorbidity, four of which died from pneumonia, one from congestive cardiac failure and the remaining patient from an unspecified cause. In these six patients the range of hospital stay was 6-105 days. Three patients died following infrainguinal bypass surgery, two from congestive cardiac failure and one from sepsis with an inpatient stay range of 5-24 days. One patient died

at 6 days following an infrainguinal angioplasty from an unspecified cause. Another died from a myocardial infarction following a MLLA at 22 days. One patient developed acute kidney injury and died (considered unfit for dialysis) 41 days following a suprainguinal angioplasty. Finally, one patient died 6 days after an aorto-bifemoral bypass having developed gut ischaemia. Table 2.4.9 documents medical and surgical inpatient morbidity.

Table 2.4.9 Inpatient morbidity during the index admission in the BASIL-PCS.

Medical Morbidity	**n=259**
Anaemia requiring transfusion of blood product	17 (6.6%)
Cardiac (Atrial fibrillation (new), MI, CCF)	8 (3.1%)
Sepsis (Respiratory, Urinary)	15 (5.8%)
Acute Kidney Injury	8 (3.1%)
Surgical Site Infection (Clavien-Dindo Grade II. Antibiotics only)	4 (1.5%)
Glycaemic Instability (requiring escalation of therapy in diabetics only)	9 (3.5%)
Gastro-intestinal bleeding	3 (1.2%)
Severe Electrolyte Disturbance (requiring intravenous correction)	4 (1.5%)
Gastrointestinal Disturbance (Constipation, gut ischaemia, cholecystitis, *Clostridium Dificile* infection)	3 (1.2%)
Venous thromboembolism	1 (0.4%)
Arterial thromboembolism	1 (0.4%)
Falls/Confusion/Delirium	5 (1.9%)
Surgical Morbidity	Frequency
Surgical site infection (Clavien-Dindo Grade III, requiring debridement/drainage)	3/121 (2.5%)
Bleeding (Clavien-Dindo Grade III, requiring surgical haemostasis)	2/121 (1.7%)
False aneurysm (Clavien-Dindo Grade III, following endovascular procedure)	2/97 (2.1%)

**Some patients had multiple complications*

Re-admissions

In the 30-days following discharge, 62 patients (62/249, 24.9%) represented to hospital. Some of which required multiple re-admissions in this timeframe. Common reasons for re-admission included progression of CLTI requiring further treatment (27 cases), sepsis (11 cases), surgical site infection (9 cases) and pain (5 cases). Further details regarding aetiology of re-admission can be seen in Table 2.4.10. Re-admission was equally high across all patient subgroups (Kruskal-Wallis, p=0.4).

The majority of patients who represented with worsening rest pain or tissue loss following primary BASIL-PCS admission were secondary to endovascular treatment failure or worsening tissue loss following previous debridement. Following endovascular treatment failure; three patients required infrainguinal bypass surgery, four required MLLA, three had further infrainguinal endovascular treatment, another had distal trash/emboli from following a suprainguinal angioplasty and stent, two patients represented with claudication following one infrainguinal and one suprainguinal angioplasty. Eleven patients were readmitted following revascularisation or foot debridement requiring further debridement or minor amputation to facilitate healing. One patient required revision from BKA to AKA due to stump necrosis. Two patients represented having been managed conservatively on the initial BASIL-PCS admission and were treated with MLLA.

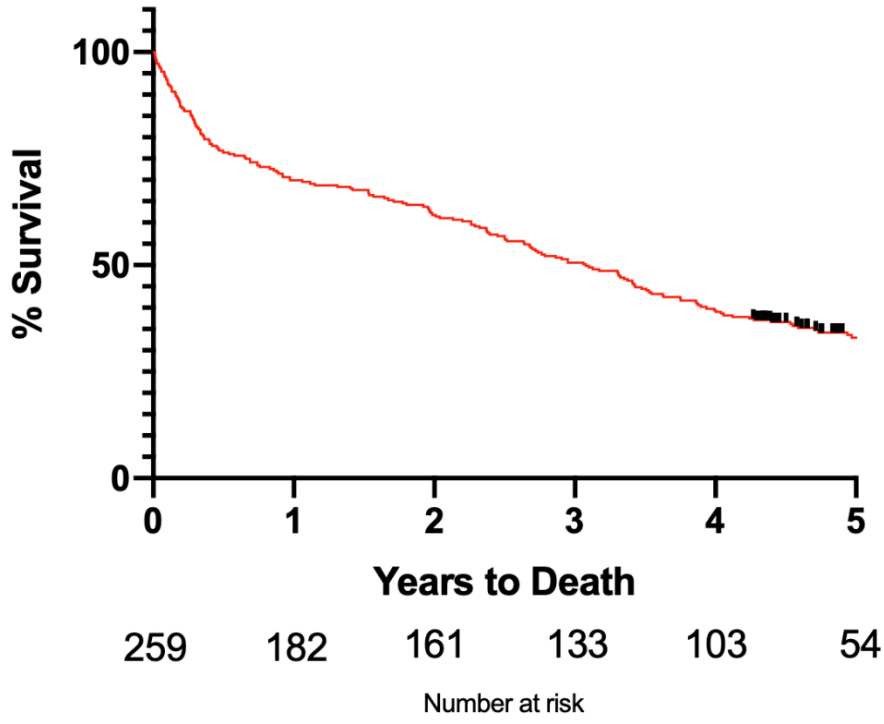
Table 2.4.10 Causes of readmission to hospital <30 days from discharge in the BASIL-PCS.

MEDICAL CAUSES FOR READMISSION	
Reason for admission	Frequency n=245
Falls	4 (1.6%)
Cellulitis	4 (1.6%)
Clostridium difficile Colitis	2 (0.8%)
Cardiac (MI, AF, CCF)	6 (2.4%)
Sepsis (medically related, urinary/respiratory)	11 (4.5%)
Stroke related disease	1 (0.4%)
Failure to cope at discharge destination	2 (0.8%)
Acute Kidney Injury	4 (1.6%)
VTE	1 (0.4%)
SURGICAL CAUSES FOR READMISSION	
Reason for admission	Frequency n=245
Haematoma	2 (0.8%)
Pain	5 (2.0%)
Worsening or non-resolving symptoms of CLTI	27 (11.0%)
Major bleeding requiring surgical haemostasis	2 (0.8%)
Foot sepsis requiring drainage	3 (1.2%)
Gastro-Intestinal complication (Ischaemia, Cholecystitis)	2 (0.8%)
Surgical Site Infection	9 (3.7%)
Acute Limb Ischaemia	1 (0.4%)
Fractured Neck of Femur	1 (0.4%)
Haematuria	1 (0.4%)

Long-term Analyses

In terms of the whole cohort, overall survival was estimated at 1 year (69.9%), three years (50.6%) and five years (32.9%), see Figure 2.4.7.

Figure 2.4.7 Overall Survival in the total cohort of BASIL-PCS patients.



From the initial recruitment stage to the 7th of December 2020, 177 out of 259 patients (68.3%) have died. The most common causes of death were of cardiac origin (20.3%) and bronchopneumonia (17.3%). Other causes of death are listed in Table 2.4.11. Unfortunately, a cause of death could not be identified in more than a third of patients. These accounted for deaths in the community and we do not have access to data stored by The Office of National Statistics to obtain it (https://www.ons.gov.uk).

Table 2.4.11 Causes of death in patients recruited into the BASIL-PCS.

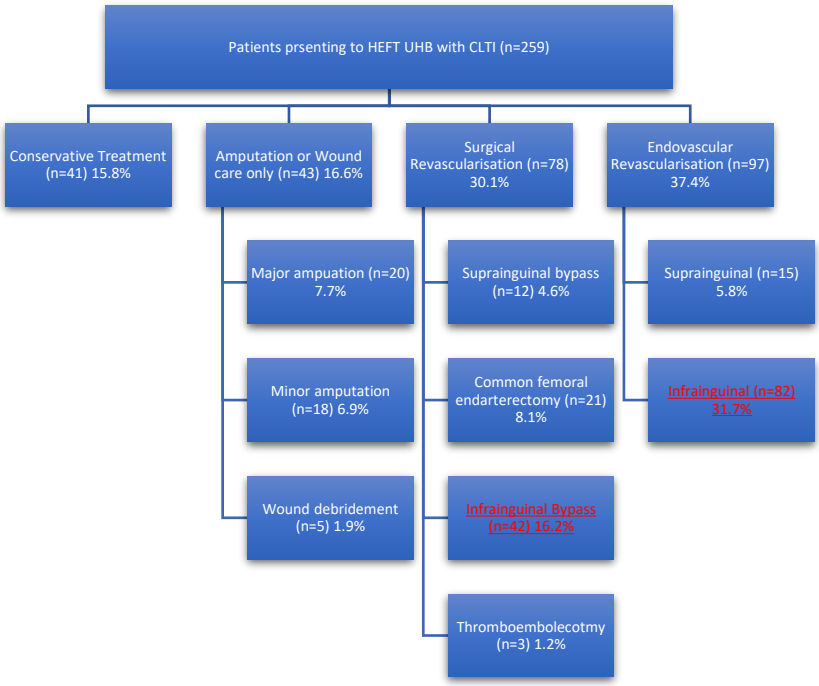
Cause	**Number n=177**
Unknown cause	56 (31.6%)
Malignancy	9 (5.1%)
Coronavirus - 19	4 (2.3%)
CLTI – palliative symptoms	4 (2.3%)
"Old age"	3 (1.7%)
Ruptured aortic aneurysm	1 (0.6%)
Cardiac (Myocaridal infarction, congestive cardiac failure, arrythmia)	36 (20.3%)
Renal failure	6 (3.4%)
Bronchopneumonia	31 (17.5%)
Mesenteric Ischaemia	2 (1.1%)
Sepsis other than lung (urinary tract, cellulitis, bacteraemia, etc.)	16 (9.0%)
Hepatic failure	1 (0.6%)
Cerebrovascular Accident	1 (0.6%)
Multiorgan failure	6 (3.4%)
Venous Thromboembolism	1 (0.6%)

Comparing those undergoing infrainguinal revascularisation

The following section will focus on those patients who were selected for infrainguinal revascularisation as their "first" revascularisation procedure following initial presentation during the BASIL-PCS recruitment period on an intention to treat basis.

Figure 2.4.8 demonstrates the patients analysed in this subsection. Participants are highlighted in red.

Figure 2.4.8 Flow diagram delineating patients selected for infrainguinal subgroup analysis.



With the exception of a higher proportion of diabetics in the BET group (BET 52/82, 63.4% vs. Bypass 15/42, 35.7%, χ^2 0.395, p=.0001) patients were comparable in terms of comorbidity, presenting symptoms and medications (Table 2.4.12).

From a haemodynamic perspective, the median ABPI was significantly higher in the group receiving BET (BET 0.59 vs Bypass 0.41, p=.007). Median PEDIS scores and WIfI clinical grades were similar. GLASS overall grades were worse in those undergoing surgical bypass with over 90% of patients calculated at GLASS grade III. This was largely due to more patients with severe femoropopliteal disease (GLASS femoropopliteal grade IV). Foot run off was significantly better in those undergoing bypass (p=.002, see Table 2.4.13 for haemodynamic and scoring data). Technical details including early failures have already been discussed in an earlier section.

Table 2.4.12 Baseline demographics in those undergoing infrainguinal revascularisation in the BASIL-PCS.

MEASURE	BET n=82	Bypass n=42	p value
Male sex	48 (58.5%)	31 (73.8%)	0.09
Age (median, IQR)	74 (64.8–83.5)	75 (67.6–82.9)	
Medical History			
Chronic Kidney Disease	26 (31.7%)	12 (28.6%)	0.7
Dialysis dependence	5 (6.1%)	1 (2.4%)	0.8
Stroke/TIA	13 (15.9%)	6 (14.3%)	0.8
Myocardial Infarction	15 (18.3%)	9 (21.4%)	0.7
Angina	18 (21.9%)	10 (23.8%)	0.8
Coronary Artery Bypass Grafting	10 (12.2%)	9 (21.4%)	0.2
Percutaneous Coronary Intervention	8 (9.8%)	3 (7.1%)	0.6
Diabetes	52 (63.4%)	15 (35.7%)	0.001
Insulin dependence	33/52 (63.5%)	6/15 (40.0%)	0.003
Smoking Status			
Current	20 (24.4%)	13 (31.0%)	.4
Ex	40 (48.8%)	22 (52.4%)	
Never	22 (26.8%)	7 (16.7%)	
Obesity (Body Mass Index >30)	13 (15.9%)	2 (4.8%)	.07
Mobility			
Independent	21 (25.6%)	14 (33.3%)	.3
Walks with aides	48 (58.5%)	27 (64.3%)	
Wheelchair bound	11 (13.4%)	1 (2.4%)	
Bed bound	1 (1.2%)	0 (-)	
Unavailable	1 (1.2%)	0 (-)	

Clinical Status			
Rest pain	56 (68.3%)	36 (85.7%)	.2
Tissue loss	73 (89.0%)	32 (76.2%)	.2
Both	65 (79.3%)	30 (71.4%)	.3
Medical Therapy			
Aspirin	48 (58.4%)	25 (59.5%)	.9
Clopidogrel	24 (29.3%)	9 (21.4%)	.4
Other antiplatelet agent	2 (2.4%)	3 (7.1%)	.2
Cholesterol reducing agent	62 (75.6%)	33 (78.6%)	.7
Anti-hypertensive agent	70 (85.4%)	31 (73.8%)	.1
Warfarin	7 (8.5%)	5 (11.9%)	.5
Direct Oral Anticoagulant	4 (4.9%)	0 (-)	.1
Considered "BMT"*	54 (65.9%)	30 (71.4%)	.5

*BMT – Best medical therapy as stipulated in NICE CG147[22].

Median length of stay during index BASIL-PCS admission was similar in both groups (BET 11 days, IQR 6 – 21 vs. Bypass 12 days, IQR 8.3 – 21.8, Mann-Whitney U; p=0.2). There were two inpatient deaths in the bypass group, both from post-operative congestive cardiac failure. There was one inpatient death in the BET group from an unknown cause.

Inpatient morbidity was equivalent between the groups (BET 24/82, 29.3% vs. Bypass 10/42, 23.8%, χ^2 0.416, p=0.5). Although 24 patients who received BET and 10 patients who received a bypass experienced in hospital morbidity, some patients experienced multiple significant health problems (Table 2.4.14).

Table 2.4.13 Haemodynamic and Limb assessments in those undergoing infrainguinal revascularisation in the BASIL-PCS.

MEASURE	BET	Bypass	p value
Median ABPI (IQR)	0.59 (0.45 – 0.74)	0.41 (0.35 – 0.55)	.007
PEDIS (Median, IQR)	n=81 8 (5 – 9)	n=41 7 (2 – 8)	.2
WIfI	n=74	n=34	
WIfI Stage I	11 (14.9%)	2 (5.9%)	.3
WIfI Stage II	19 (25.7%)	10 (29.4%)	
WIfI Stage III	21 (28.4%)	13 (38.2%)	
WIfI Stage IV	23 (31.1%)	9 (26.5%)	
GLASS	n=80	n=41	
Femoropopliteal Grade			
FP Grade 0	6 (7.5%)	2 (4.9%)	.004
FP Grade I	8 (10.0%)	1 (2.4%)	
FP Grade II	9 (11.3%)	0 (-)	
FP Grade III	14 (17.5%)	1 (2.4%)	
FP Grade IV	43 (53.8)	37 (90.2%)	
Infrapopliteal Grade			
IP Grade 0	31 (38.8%)	16 (39.0%)	.8
IP Grade I	3 (3.8%)	0 (-)	
IP Grade II	20 (25.0%)	11 (26.8%)	
IP Grade III	14 (17.5%)	6 (14.6%)	
IP Grade IV	12 (15.0%)	8 (19.5%)	
Overall Grade			
Overall Grade I	7 (8.8%)	1 (2.4%)	.001
Overall Grade II	21 (26.3%)	2 (4.9%)	

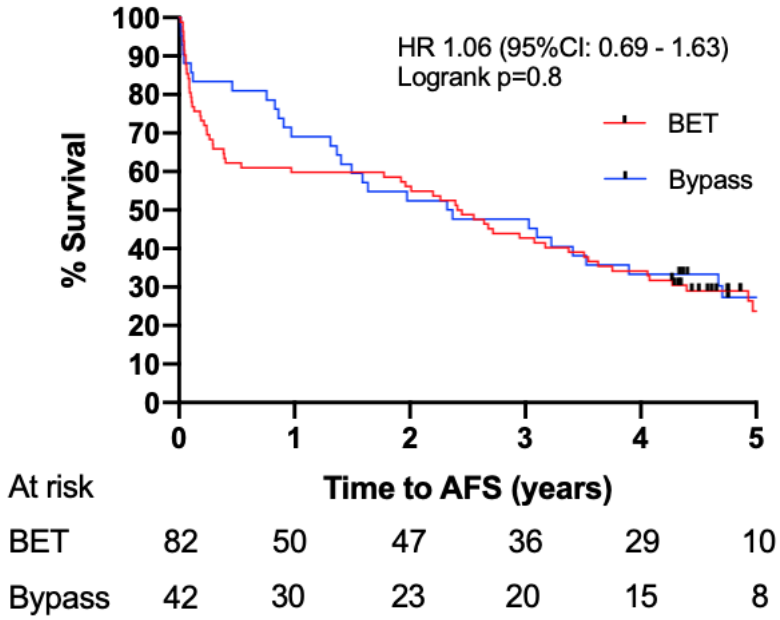
Overall Grade III	52 (65.0%)	37 (90.2%)	
Pedal Modifier	n=78	n=39	
Pedal Modifier P0	6 (7.7%)	15 (38.5%)	.002
Pedal Modifier P1	43 (55.1%)	13 (33.3%)	
Pedal Modifier P2	28 (35.9%)	11 (28.2%)	

Table 2.4.14 Inpatient morbidity in those undergoing infrainguinal revascularisation in the BASIL-PCS.

Morbidity	**BET n=82**	**Bypass n=42**	**p value**
Sepsis	5 (6.1%)	3 (7.1%)	NS
Blood Transfusion	3 (3.7%)	3 (7.1%)	NS
Glycaemic instability	6 (7.3%)	0 (-)	NS
Haematoma (post intervention)	3 (3.7%)	3 (7.1%)	NS
Bleeding requiring intervention	2 (2.4%)	1 (2.4%)	NS
Acute Kidney Injury	4 (4.9%)	0 (-)	NS
Cardiac (myocardial infraction, congestive cardiac failure)	1 (1.2%)	1 (2.4%)	NS
Gastrointestinal	1 (1.2%)	0 (-)	NS
Surgical site infection requiring intervention	0 (-)	1 (2.4%)	NS
Significant fall leading to injury	0 (-)	1 (2.4%)	NS
Total number of patients experiencing morbidity	24 (29.3%)	10 (23.8%)	.5

AFS was initially better in those receiving bypass surgery estimated at 69.0%, 47.6% and 27.3% at one, three and five years respectively, in comparison to BET (59.8%, 42.7% and 23.7% at the same timepoints). Overall there was no difference in AFS out to five years (HR 1.069 (95%CI:0.69 – 1.63), Log-rank p=0.8, Figure 2.4.9)

Figure 2.4.9 AFS in those receiving best endovascular treatment or bypass surgery for CLTI secondary to infrainguinal disease in the BASIL-PCS.



Overall survival was similar in both groups out to five years (HR 1.14, 95%CI: 0.71 – 1.83, Log-rank p=0.6, Figure 2.4.10). Survival estimates for those undergoing BET were 78.0%, 58.5% and 38.2% at one, three and five years respectively. Those undergoing bypass surgery had survival estimates of 81.0%, 61.9% and 44.6% at the same time points.

There were also no significant differences in limb salvage out to five years (HR 1.01, 95% CI: 0.53 – 1.94, Log-rank p=1.0, Figure 2.4.11). There were no significant differences in MALE (HR 1.07, 95%CI: 0.64 – 1.78, Logrank p=0.8, Figure 2.4.12) or FF-R (HR 0.75, 95%CI: 0.38 – 1.46, Logrank p=0.4, Figure 2.4.13).

Figure 2.4.10 OS in those receiving best endovascular treatment or bypass surgery for CLTI secondary to infrainguinal disease in the BASIL-PCS.

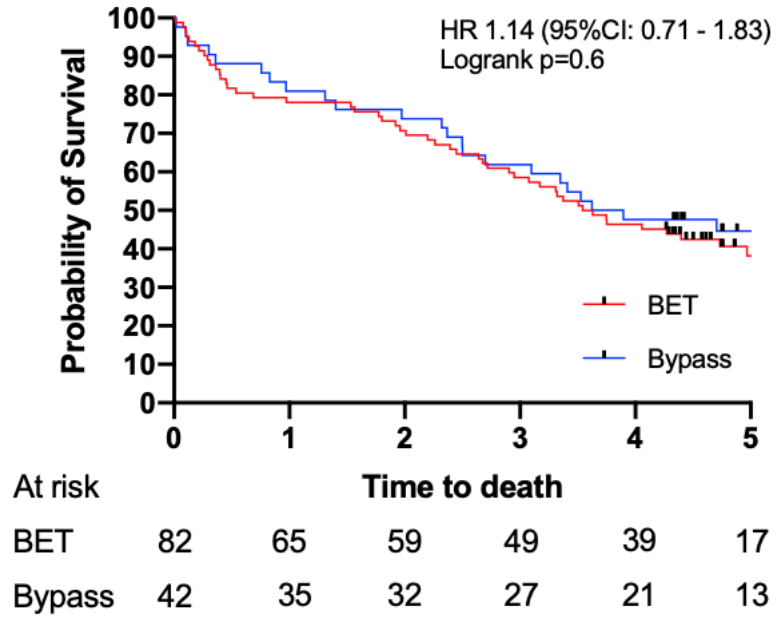


Figure 2.4.11 Limb Salvage in those undergoing infrainguinal revascularisation in the BASIL-PCS.

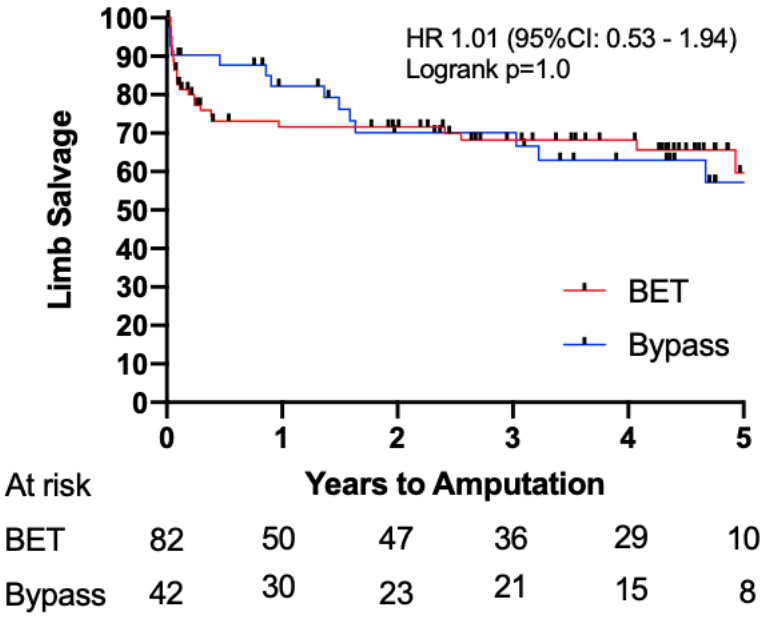


Figure 2.4.12 Freedom from Major Adverse Limb Event in those undergoing infrainguinal revascularisation in the BASIL-PCS.

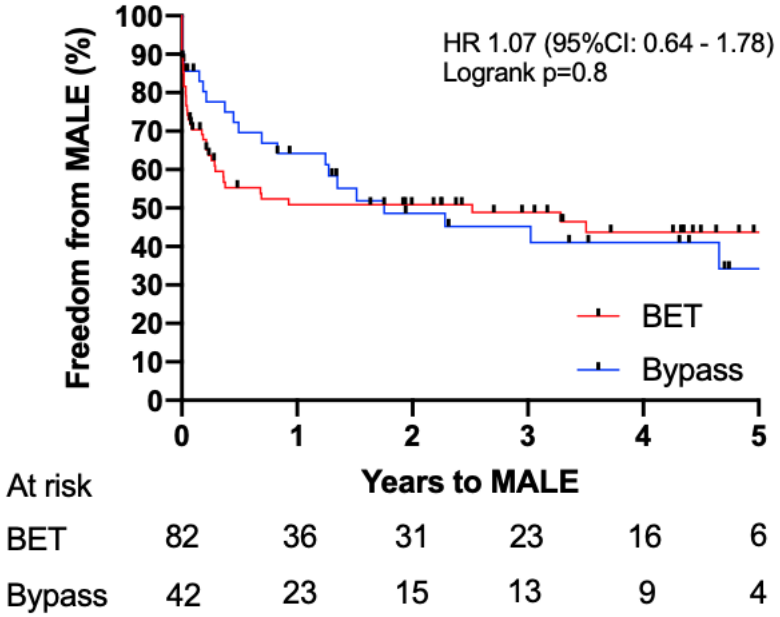
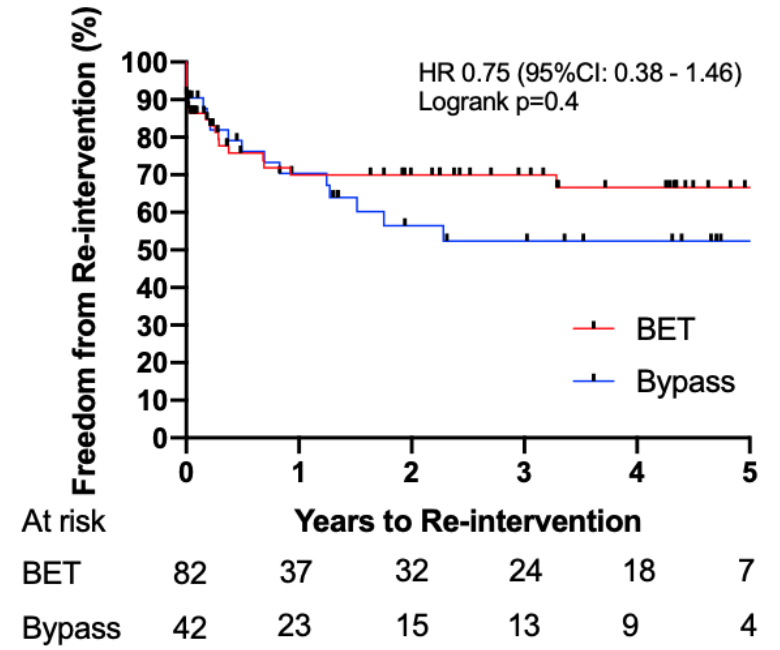


Figure 2.4.13 Freedom from Re-intervention in those undergoing infrainguinal revascularisation in the BASIL-PCS.



Subgroup analysis of those with infra-popliteal disease receiving infrainguinal revascularisation

In total, 77 patients underwent revascularisation secondary to infrapopliteal +/- femoropopliteal disease (51 BET, 26 bypass). In terms of assessment and risk, both groups had high limb threat (Median WIfI 3 in both groups, Mann-Whitney U, p=0.9), however those undergoing bypass had higher GLASS total clinical grades (Mann-Whitney U, p=0.04).

In terms of outcome there were no differences in AFS (HR 1.01, 95%CI: 0.61 – 1.70, Log-rank p=1.0), OS (HR 1.12, 95%CI: 0.64 – 1.95, Log-rank p=0.6), FF-R (HR 0.83, 95%CI: 0.35 – 1.97, Log-rank p=0.7), MALE (HR 1.12, 95%CI: 0.58 – 2.15, Log-rank p=0.6) or LS (HR 0.93, 95%CI: 0.43 – 2.04, Log-rank p=0.9) out to five years.

Fourteen patients undergoing infrainguinal endovascular treatment underwent arterial reintervention. The majority of which underwent repeat infrainguinal endovascular revascularisation (7/14, 50%). Four patients had surgical bypass. Two patients went to theatre as an emergency for pseudoaneurysm repair post puncture. One final patient had an urgent embolectomy following failed intervention. Reintervention in those having surgical bypass was predominated by endovascular treatment of graft stenoses (6/10, 60%) with four other patients undergoing urgent procedures during the index admission to salvage the limb or graft (three thrombo-embolectomies, 1 severe bleeding requiring redo graft).

Subgroup analysis of those selected for conservative therapy or primary amputation

The flow diagram below delineates the patients selected for analysis in this section which are highlighted in red (Figure 2.4.12).

Patients undergoing conservative therapy tended to be older, but otherwise those selected for MLLA, conservative therapy and infrainguinal revascularisation were broadly similar (Table 2.4.14).

In terms of WIfI clinical assessment there were no significant differences in wound component (Kruskal-Wallis, p=0.09), ischaemic status (Kruskal-Wallis, p=0.3), foot infection (Kruskal-Wallis, p=0.4) or total WIfI clinical grade (Kruskal-Wallis, p=0.2). There was a trend toward a higher median wound score in those undergoing MLLA (MLLA, median score 2 vs. Infrainguinal revascularisation and conservative treatment 1). All three groups had a median total WIfI grade of 3 which signifies moderate risk of limb threat (Figure 2.4.15).

Figure 2.4.14 Flow diagram showing patient selection for those receiving or choosing conservative treatment or amputation.

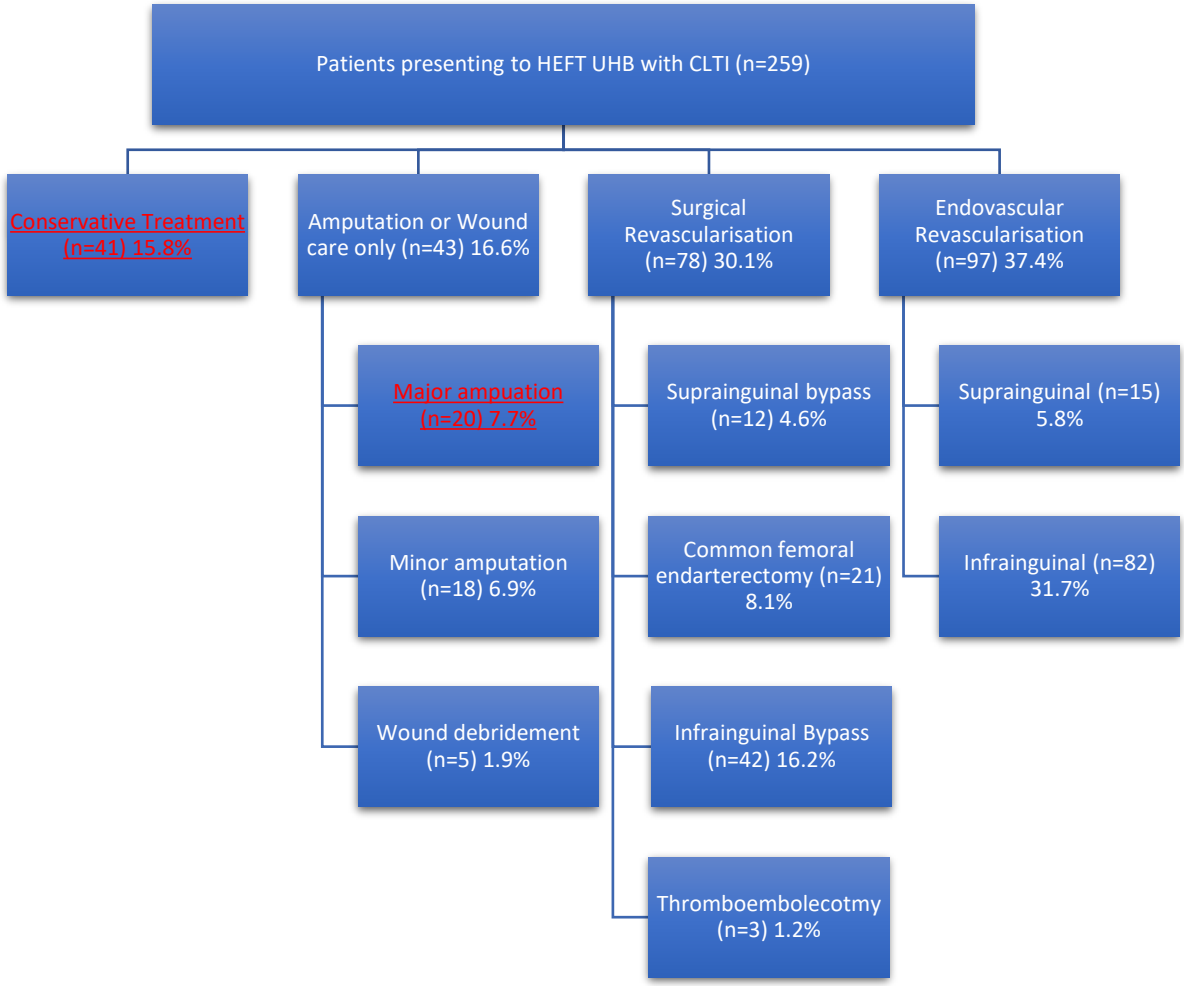


Table 2.4.15 Comparison of baseline demographics in those patients selected for conservative treatment, MLLA and infrainguinal revascularisation in the BASIL-PCS.

MEASURE	**Conservative n=41**	**MLLA n=20**	**Infrainguinal revascularisation n=124**	**p value**
Male sex	22 (53.7%)	11 (55.0%)	79 (63.7%)	.45
Age (median, IQR)	82.3 (73.5 – 86.3)	74.9 (65.6 – 83.9)	74.3 (65.3 – 82.9)	.02
Medical History				
Chronic Kidney Disease	20 (48.8%)	7 (35.0%)	38 (30.6%)	.1
Dialysis dependence	0 (-)	0 (-)	1 (0.8%)	.2
Stroke/TIA	10 (24.4%)	4 (20.0%)	19 (15.3%)	.4
Myocardial Infarction	7 (17.1%)	4 (20.0%)	24 (19.4%)	.9
Angina	6 (14.6%)	4 (20.0%)	28 (22.6%)	.6
CABG	2 (4.9%)	3 (7.3%)	19 (15.3%)	.2
PCI	4 (9.8%)	1 (5.0%)	11 (8.9%)	.8
Diabetes	23 (56.1%)	12 (60.0%)	67 (54.0%)	.7
Insulin dependence	10 (24.4%)	7 (35.0%)	39 (31.5%)	.7
Smoking Status				
Current	9 (21.9%)	6 (30.0%)	33 (26.6%)	.7
Ex	24 (58.5%)	7 (35.5%)	62 (50.0%)	
Never	8 (19.5%)	7 (35.5%)	29 (24.4%)	
Obesity (Body Mass Index >30)	2 (4.9%)	2 (10.0%)	15 (12.1%)	.4

Mobility				
Independent	8 (19.5%)	3 (15.0%)	35 (28.2%)	.1
Walks with aides	24 (58.5%)	10 (50.0%)	75 (60.5%)	
Wheelchair bound	7 (17.1%)	6 (30.0%)	12 (9.7%)	
Bed bound	2 (4.9%)	1 (5.0%)	1 (0.8%)	
Unavailable	0 (-)	0 (-)	1 (0.8%)	
Clinical Status				
Rest pain	27 (65.8%)	12 (60.0%)	91 (73.4%)	.6
Tissue loss	31 (75.6%)	17 (85.0%)	105 (84.7%)	.06
Medical Therapy				
Aspirin	18 (43.9%)	10 (50.0%)	73 (58.9%)	.2
Clopidogrel	11 (26.8%)	8 (40.0%)	33 (26.6%)	.5
Other antiplatelet agent	1 (2.4%)	0 (-)	5 (4.0%)	.6
Cholesterol agent	27 (65.8%)	12 (60.0%)	95 (76.6%)	.2
Anti-hypertensive agent	30 (73.2%)	11 (55.0%)	101 (81.5%)	.03
Warfarin	9 (21.9%)	1 (5.0%)	12 (9.7%)	.07
DOAC	2 (4.9%)	1 (5.0%)	4 (3.2%)	.9
Considered “BMT”*	24 (58.5%)	9 (45.0%)	84 (67.7%)	.1

*BMT according to NICE CG147[22]

In terms of anatomical staging, all three groups had severe femoro-popliteal disease (Kruskal-Wallis, p=0.3), however those treated conservatively tended to have more severe infrapopliteal disease (Kruskal-Wallis, p=0.05). This however did not affect the overall GLASS stage which predicted high levels of limb threat in all three categories (Kruskal-Wallis, p=0.7, Figure 2.4.16).

Figure 2.4.15 A comparison of Wound, Ischaemia, Foot infection scores in patients selected for conservative treatment, MLLA and infrainguinal revascularisation in the BASIL-PCS.

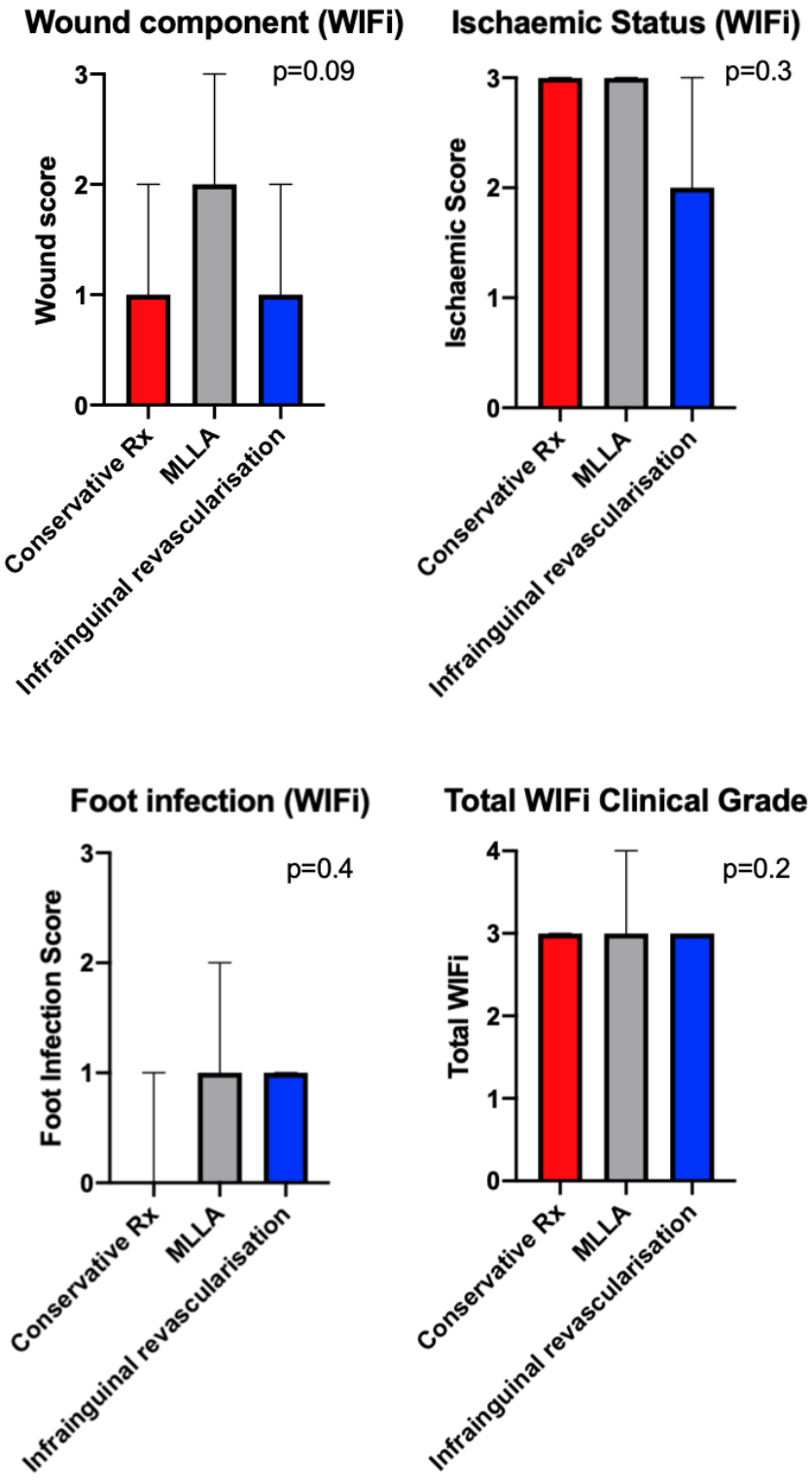
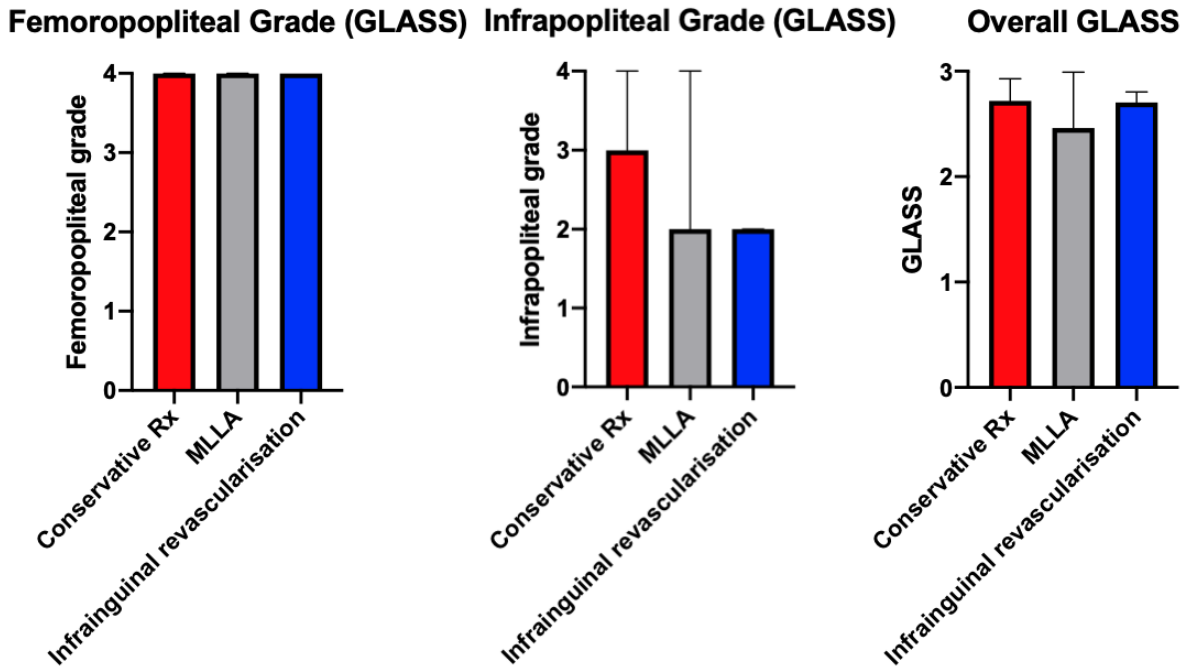
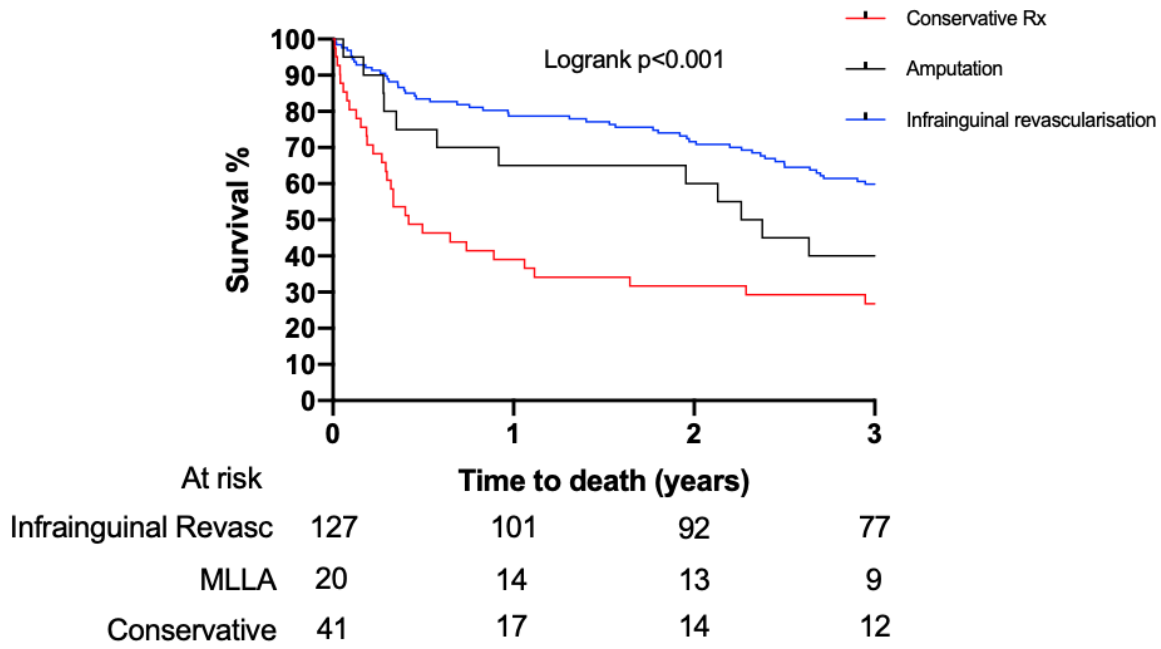


Figure 2.4.16 A comparison of Global Anatomic Staging System (GLASS) scores in patients selected for conservative treatment, MLLA and infrainguinal revascularisation in the BASIL-PCS.



Overall survival in the group of patients selected for, or choosing conservative treatment was poor, estimated at a median of 0.42 years (5.04 months). Equally, longer-term survival was relatively low (39.0% 1-year, 26.8% 3-years). Overall survival was much worse in this group compared to those selected for revascularisation (median survival 3.6 years), or even MLLA (median survival 2.3 years) on index BASIL-PCS admission (Log-rank p<.001, Figure 2.4.17).

Figure 2.4.17 Comparison of overall survival in those selected for infrainguinal revascularisation, index admission MLLA or conservative treatment.



Impact on the National Health Service and HEFT UHB

Accounting for multiple re-admissions to hospital, during the total time period of study (June 2014 to December 2020) patients enrolled into BASIL-PCS accounted for 16,031 hospital bed days. Of those days, 15,598 days were spent on the ward, 323 days in a high dependency setting and 110 days in an intensive care setting. The estimated cost of caring for these 259 patients is approximately £8,726,906.50 (see Table 2.4.16) from presentation to the end of the follow up period (7th December 2020). This equates to a mean of £33,694 per patient. Costing relating specifically to infra-popliteal procedures and amputation has been covered in more detail in another chapter of this Thesis.

Table 2.4.16 Cost estimation based on admissions and In-hospital bed days for patients enrolled in the BASIL-PCS.

Metric	Total number of days	Unit cost (£)	Cost (£)
First BASIL-PCS admission			
Admissions to hospital	259	£3,208	£830,872
Ward (days)	4,605	£321	£1,478,205
Higher level of care (days)	138 HDU 16 ITU	£1,493.50	£229,999
Total for first admission	4,759	n/a	£2,539,076
Further all-cause readmissions following discharge			
Readmissions to hospital	699	£3208	£2,242,392
Ward	10,993	£321	£3,528,752
Higher level of care	185 HDU 94 ITU	£1,493.50	£416,686.50
Total for readmissions	11,272 days	n/a	£6,187,830.50
Total	**16,031 days**	**n/a**	**£8,726,906.50**

2.4.4 Discussion

Although the population we studied was heterogeneous, we have demonstrated the sobering reality of the outcomes from a CLTI cohort outside of an interventional study with highly selected patients in this "real world" analysis. Not only was mortality and limb salvage poor, but medical and surgical morbidity, re-admission to hospital and length of hospital stays remarkably high.

Generally, outcomes from the whole BASIL-PCS cohort were relatively poor. Mortality was much poorer than data quoted in the literature, 5-year mortality in the symptomatic PAD population has been quoted at 27% by Sigvant[7] (vs 67.1% in the BASIL-PCS cohort). In this review most patients were claudicants and data regarding the long-term prognosis of CLTI was sparse and of poor quality. The 'true' outcomes of patients with CLTI are likely to be presently unknown due to reporting bias, a focus on interventional groups/cohorts and a lack of prospective data on 'all comers'. A significant proportion of patients did not have a recorded cause of death, this was due to mortality recording in the community. Access to ONS data where all deaths are recorded was not available as part of the BASIL-PCS due to funding. BASIL-2 and 3 have had similar issues, in that obtaining ONS data is both expensive and prolonged (over 12-months from data query to results). The data is important to ascertain why patients with CLTI are not surviving, in particular, if it is related to their PAD or similar disease in other vascular anatomical beds.

The poor outcomes in BASIL-PCS in some part may be explained by a lack of medical optimisation. A high proportion of patients were diabetic, which is not uncommon for the general population that HEFT UHB serves. It has been reported that those with CLTI and diabetes treated with insulin therapy have similar mortality to CLTI patients without diabetes. However, patients with insulin dependent diabetes (IDDM) have poorer complete wound healing (Non-diabetic 41%, Non-insulin dependent (NIDDM) 49%, IDDM 61%, $p<0.001$) and an increase in 'RAS' (re-intervention, major amputation or re-stenosis) events (HR 1.4, 95%CI: 1.1 – 1.8) when compared to those with no diabetes or non-insulin dependent disease. This effect is most pronounced in those undergoing endovascular treatment as a 'first' revascularisation attempt[114]. Given that just over a third of patients received infrainguinal

endovascular treatment, and more than 60% had IDDM, it is unsurprising that AFS was so poor, particularly in the first 18 months following attempted endovascular revascularisation.

It is interesting that despite the results from the BASIL-1 trial, suggesting that patients with vein conduit and good life expectancy are better served with vein bypass as a revascularisation strategy that the predominant choice of at HEFT UHB was infrainguinal endovascular therapy (31.7%). In general, the unit has a treatment bias toward an 'endovascular first' strategy. This may in part be explained by a lack of access to emergency theatres which may delay intervention to an unacceptable timeframe or because of perceived lack of patient 'fitness' to withstand open surgery under regional or general anaesthesia. This lack of equipoise across the UK made it difficult to randomise patients into the BASIL-2 trial and its recruitment was prolonged and extended to mitigate for this.

The prescription of BMT was poor at point of admission. Only 62.5% of patients were taking NICE recommended therapy[22]. This is surprising, given the high prevalence of cardiovascular comorbidity and previous vascular interventions within the cohort. This may in part explain the poor OS of the total cohort (Only 50.6% alive at 3-years from index BASIL-PCS admission). However, this study was not powered, nor is sufficient in-patient numbers to detect survival differences apparent from the prescription of BMT. Given the nature of electronic follow-up used in the BASIL-PCS it was not possible to assess adherence to medications in the long-term.

Haemodynamic data capture within the BASIL-PCS was adequate. This was by far the most difficult metric to record, given that some patients received urgent treatment overnight directly following admission before a member of the research team could complete the baseline assessment and BASIL-2 screening. It was not possible given the staffing to have a '24/7' presence with the vascular team to enable 100% haemodynamic data capture. The measurement

of haemodynamic indices seems to be falling out of favour in modern vascular practice outside of research. Even during the recruitment phase of BASIL-2 some units in the UK were not recording ABPI measurements as part of their 'routine clinical practice' and therefore did not submit this data for analysis. This has an impact on the proposed 'PLAn' principle suggested by the GVG[13,14] as haemodynamic measurement forms an integral part of the WIfI assessment which has been well validated[115–118] as predictive tool.

In terms of WIfI, of the total cohort, 63.1% were classified as WIfI stage 3 or 4, which signifies moderate to high risk of MLLA and very little benefit of revascularisation[29]. It unsurprising that long-term outcomes were so poor given this fact.

Although MRA is the recommended 'gold standard' investigation in CLTI it is currently unavailable at our unit. CTA was the most commonly used imaging tool for both initial imaging and definitive imaging prior to treatment decision making. This may explain why many patients with infrainguinal disease went on to have endovascular treatment, as during subsequent DSA, significant lesions were treated in the same sitting rather than a 'stop and discuss' mantra. Time to imaging may have had an impact on time to treatment as there are typically delays, particularly in obtaining a DSA, regrettably we did not measure this metric in the BASIL-PCS data capture form. Although, the median time to treatment in those receiving infrainguinal revascularisation was just in line with current national guidance[113] (five days from admission).

GLASS scores were calculated retrospectively for most patients where imaging was available. Our research group has recently validated GLASS using the BASIL-1 cohort were angiography was available[55] and demonstrated that GLASS was associated with outcomes for patients undergoing endovascular treatment, but not bypass surgery. Others have found that GLASS stage 3 is strongly associated with reduced OS, AFS and FF-R in both endovascular and bypass

cohorts[119]. There have been recent mixed reports of the effectiveness of GLASS at predicting outcomes in both the haemodialysis population[120] and in those requiring infrapopliteal, endovascular revascularisation[121]. All of these studies were retrospective, and clearly more research is required to refine best use of this system. To improve the ascertainment of GLASS stage scoring in our cohort we opted to use CTA as an imaging modality to assess patients. We accept that this is not yet a validated method of assessing the TAP. Given the nature of CTA, scoring of the infrapopliteal segment may have been overestimated, particularly in the presence of calcification and the determination of pedal run-off.

It was surprising that almost a third of patients did not undergo revascularisation in the cohort. These decisions seemingly were made based on age, comorbidity or factors not measured by the BASIL-PCS given that there were no significant differences in patient clinical (WIfI) or anatomical factors (GLASS). Patients receiving no intervention other than wound care and pain control had severely limited survival, even in comparison to those undergoing MLLA at index BASIL-PCS admission.

Immediate treatment failure in those undergoing infrainguinal endovascular intervention was much higher than in those undergoing bypass surgery (16.0% vs. 7.3%). This likely reflects a group of patients with severe disease where endovascular treatment failure was expected, but still attempted in desperation to prevent limb loss. This was also reflected in early treatment failures with re-admissions to hospital within thirty days, multiple patients required repeat revascularisation or MLLA following endovascular treatment failure. Whether these patients should have had an alternative revascularisation strategy or primary MLLA is a matter of debate.

Surgical site infection (SSI) in the cohort was much lower than is currently reported in patients undergoing lower limb vascular surgery[11,122]. The combined rate of SSI in the BASIL-PCS was 4.0%. In the PCS patients did not provide consent for clinical or wound follow-up outside of normal clinical practice. The 'electronic' follow up used is not an accurate way of measuring SSI rates which are likely under reported in cohorts such as this due to poor coding and lack of access to general practice data.

Similarly, the incidence of acute kidney injury was low in the total cohort of patients (3.1%). AKI rates were recorded from patient discharge summaries, when mentioned. This has likely led to an under-representation in the study. Ongoing, prospectively documented biochemistry or urine output measurements in line with NICE recommended criteria for the detection of AKI[123] would be a more preferable and accurate measure, however such detail was outside the scope, funding and manpower of this study.

One of the main purposes of the BASIL-PCS was to determine the generalisability of BASIL-2 to the CLTI cohort as a whole. At HEFT-UHB we randomised 16 patients in total during the BASIL-PCS data collection period. This represents 6.2% of the whole cohort and 14.4% of those with infrapopliteal disease. Recruitment into BASIL-2 was difficult, the study overran and finished recruitment early, focussing on extended follow-up with the patients that have been randomised in order to maintain adequate statistical power. Recruitment was less than anticipated for a variety of reasons; the COVID-19 pandemic, lack of clinician equipoise due to bias toward a particular treatment strategy, perceived lack of operating time and space to perform infrapopliteal bypass and lack of research support staff to adequately complete patient follow-up.

At HEFT-UHB, over one third of patients with infrapopliteal disease had endovascular treatment outside of the trial, indicating a strong preference toward endovascular treatment as a 'first' revascularisation strategy. Another barrier to recruitment was the severity of disease and unfitness for intervention in the cohort, 32.4% of patients with infrapopliteal disease were managed conservatory with analgesics and dressings or underwent MLLA. We believe from an academic standpoint there is intellectual equipoise regarding the optimal 'first' revascularisation strategy in this patient group and the BASIL-2 trial will be a key component in determining this. However, it seems that from the BASIL-PCS data a high proportion of patients are simply too unfit or have disease that is too severe to contemplate revascularisation. It is unclear if such results are generalisable to other UK vascular units.

We did not demonstrate significant difference in long-term outcomes in terms of AFS, OS, FFR, LS or freedom from MALE in those undergoing infrainguinal or infrapopliteal endovascular or bypass treatment. This is in keeping with data published from both BASIL-1 and a contemporary series of patients with CLTI secondary to infrapopliteal disease[57,110].

Although AFS was similar out to 5 years in those undergoing infrainguinal revascularisation a steep, early decline was seen in patients undergoing endovascular treatment. This can be explained by a similar pattern in early limb loss in this group. One theory is that these patients underwent 'salvage' endovascular treatment, in that treatment failure and subsequent amputation was likely at presentation however the treating clinician and/or patient were unaccepting of this without an attempt to rescue. Whether such patients would be better served by a primary amputation is controversial and generally divides the opinions of vascular surgeons.

Freedom from reintervention was statistically similar in both groups however, there seemed to be a trend towards a higher late, reintervention rate in those undergoing surgical bypass. The majority of re-interventions in this group were endovascular attention to the bypass graft to maintain patency. Patients undergoing bypass surgery are enrolled into graft surveillance programmes (currently there is no surveillance for those treated with infrainguinal endovascular treatment) which may explain this increase in late reintervention. It must be noted that the number at risk after 2 years in both groups in terms of survival (FFR) is diminished so these results must be interpreted with caution.

Patients undergoing infrainguinal endovascular treatment were more likely to be diabetic which may explain the higher rate of early amputation in this group as eluded to above. However, patients receiving bypass surgery had lower ABPI, more severe femoropopliteal disease (resulting in higher WIfI stage) but better pedal run off than those receiving endovascular treatment. It would seem in this cohort that patients with CLTI are likely to succumb to sepsis (medical causes), cardiovascular disease or malignancy at a rate exceeding data seen in BASIL-1[9] (OS at 5 years 38.2% in those receiving BET vs. 44.6% in those receiving bypass). Patient reported outcomes such as relief from ischaemic rest pain, wound healing, freedom from symptoms of CLTI and HRQoL may be more important in determining the most effective 'first' revascularisation strategy rather than 'hard' clinical endpoints such as AFS. Unfortunately, we did not have the means, or ethical cover to provide this level of detailed clinical follow-up in the BASIL-PCS. Best medical therapy, early disease detection, education in primary care of both practitioners and patients and risk factor modification are all likely to be more effective at improving long term survival and more arbitrary clinical endpoints in patients with CLTI.

In-hospital morbidity in both groups of patients was similar, but unacceptably high (BET 24/82, 29.3% vs. Bypass 10/42, 23.8%; p=0.5). This was largely due to medical, rather surgical

aetiology such as sepsis, anaemia, acute kidney injury and glycaemic instability. This may suggest that a more holistic approach to patient care and regular input of senior medical physicians in the care of patients with CLTI is desirable to reduce morbidity at our unit. Such input may also reduce the re-admissions to hospital within the thirty days following discharge which was also high (24.9%). In total, our cohort of 259 patients accounted for a staggering 16,031 hospital bed days during the study period. Reducing readmissions and hospital stays is likely to have a positive impact on patient outcomes as well as institutional finances.

We also presented outcomes for those patients who were deemed inappropriate for revascularisation, either due to an unsalvageable limb or subjective lack of fitness or technical solution to withstand revascularisation. This group of patients are not adequately represented in the current literature. Outcomes in this group were unsurprisingly poor with survival estimated at 39.0% at 1 year.

Assessing patient 'fitness' is often challenging. In CLTI there are no performance criteria or threshold for fitness to aid revascularisation decisions. In the BASIL-PCS patient fitness was assessed by the individual consultant surgeon in charge of the patients care. Management decisions are therefore likely to be biased, based on the surgeon's treatment preferences or pre-defined subjective markers of 'fitness'. In the future, markers of frailty, cardiopulmonary testing and multi-morbidity scores may have a role to play in decision making, for the time being such measures are isolated to research studies, particularly in CLTI cohorts.

Those managed conservatively were older, had more CKD, more likely to be on anticoagulation and had worse tibial disease (in terms of GLASS IP grade) compared to those undergoing infrainguinal revascularisation or MLLA. All of which suggests a high burden of disease in these patients which likely contributed to a conservative decision by the treating physician. The

data not captured by the BASIL-PCS which may have added value was the specific decisions made at ward level or in an MDT meeting. CLTI is becoming increasingly complex to treat, patient presentations are heterogenous and decisions are often made on an individual basis in conjunction with the patients and family's preferences.

A review from 2015 documented the outcomes of 1,527 patients with untreated CLTI, the authors reported an all-cause mortality rate of 22% with a median of 1-year follow-up which is much lower than what we have demonstrated[71]. This could, in part, be explained by the high comorbid burden in our cohort, although comorbidity data was not readily available in the review mentioned above. The authors from this study hypothesize that the high intervention rate generally in CLTI makes it difficult to study this population of patients, however in our cohort 32.4% (84/259) of patients did not undergo an attempt at revascularisation during index BASIL-PCS admission. Given the endemic, worldwide explosion of diabetes, an aging population and ever-increasing pressures on healthcare systems this figure is likely to rise, therefore, we would suggest that research into the care of such patients is clearly required.

2.4.5 Limitations

During the period of study, we attempted to prospectively collect data on all consecutive presentations to our service in patients with CLTI. This was somewhat challenging for multiple reasons. Firstly, the data capture of patients undergoing day case angioplasty was problematic due to unexpected attendances and patients who attended for diagnostic imaging but received endovascular treatment in the same sitting who were then discharged home. For this reason, data was only obtained prospectively at baseline for those patients who were admitted following attempted endovascular revascularisation for reasons such as procedural complication, poor functional status, wound complexity or the requirement for further treatment. Similarly, there

were other specific examples of patients admitted as emergency, undergoing MLLA or admitted with acute on chronic limb ischaemia who perished before prospective data capture.

The collection of haemodynamic and wound data (WIfI[29] and PEDIS[30]) was also challenging due to rapid, emergency amputation or revascularisation that occurred out of hours preventing measurement taking before screening and consent. To achieve this in an emergency inpatient setting a 24-hour presence would be required which is highly resource intensive.

Data collected was representative of "real world" clinical practice and not the relatively homogenous, highly selected patients seen in randomised data sets. This being the case, any comparative results presented must by analysed with caution. Our data is inherently prone to selection bias based on the beliefs, behaviours, motivations of our surgeons and interventional colleagues as well as the availability of bed space, technology and theatre capacity. All of which are individually unique to our unit. How generalisable to other vascular units in the UK is a matter of debate, however, there are likely to be common practices that we have demonstrated.

The follow up of patients was entirely electronic, we did not have consent through the BASIL-2 trial[12] to perform prospective follow up visits either in person or by telephone. This limited the data that we were able to collect to such metrics that are collected as part of routine clinical practice in our unit. Ideally, prospective individual follow-up would have been desirable to collect detailed information regarding haemodynamic measurement, wound healing, pain cessation, disease specific and generic quality of life, health resource utilisation and health economics. The reality of doing such analyses outside of a well-funded, large randomised study is that resources at an individual level do not allow this amount of detail to be collated for 259 patients.

2.4.6 Conclusions

In summary, the BASIL-PCS provides a wealth of ‘real world’ data on patients that presented to HEFT-UHB with CLTI during the study period. The three main conclusions that can be drawn from these data are;

1. The outcomes of patients with CLTI are poor when considering all comers in totality due to high comorbid burden, advanced PAD and high proportion of patients who present unfit or unsuitable for intervention that are not included in traditional interventional studies.

2. Despite there being a unit bias at HEFT UHB toward infrainguinal endovascular therapy this did not result in improved outcomes when compared to those undergoing infrainguinal bypass. This did however, impact on the number of potentially eligible patients randomised into BASIL-2 due to lack of clinician equipoise.

3. The ongoing care of patients with CLTI presents a large financial burden on healthcare systems owing to repeat interventions, readmissions and morbidity which necessitates ongoing investment, research and public health effort to improve limb salvage, prevent such readmissions and ultimately increase the survival prospects of this challenging patient group.

2.5 PROCEDURAL AND 12 MONTH IN-HOSPITAL COSTS OF PRIMARY INFRA-POPLITEAL BYPASS SURGERY, INFRA-POPLITEAL BEST ENDOVASCULAR TREATMENT, AND MAJOR LOWER LIMB AMPUTATION FOR CHRONIC LIMB THREATENING ISCHAEMIA

Health care purchasing is at present of maximal importance given funding constraints and a drive for clinicians to demonstrate 'value' in health care, in particular health care technologies. The current evidence-base surrounding the management of CLTI secondary to IP disease and its cost to health care purchasers is relatively poor. Health care purchasing in the UK is complex and difficult to estimate. Some propose that although endovascular treatment is 'cheaper' at the outset in terms of resources, time and ward bed days, that this initial cost benefit is offset in the longer term by repeated interventions and poorer outcomes. The purpose of this section was to ascertain the in-hospital costs of IP endovascular intervention, IP surgical bypass and MLLA in East Birmingham in patients presenting with CLTI during their index admission and in the following 12-months from intervention.

2.5.1 Abstract

Introduction

Chronic limb threatening ischaemia (CLTI) is a growing global problem due to the widespread use of tobacco and increasing prevalence of diabetes. Although the financial consequences are considerable, few studies have compared the relative cost-effectiveness of different CLTI management strategies. The Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-2 trial is randomising CLTI patients to primary infra-popliteal (IP) vein bypass surgery (BS) or best endovascular treatment (BET) and includes a comprehensive within-trial cost-utility analysis. We aim to compare over a 12-month time horizon, the costs of primary IP

BS, IP best endovascular treatment (BET), and major limb major amputation (MLLA) to inform the BASIL-2 cost-utility analysis.

Methods

We compared procedural human resource (HRe) costs and total in-hospital costs for the index admission, and over the following 12-months, in 60 consecutive patients undergoing primary IP BS (n=20), IP BET (n=20), or MLLA (10 transfemoral and 10 transtibial) for CLTI within the BASIL prospective cohort study.

Results

Procedural HRe costs were greatest for BS (BS £2,551, 95% CI: £1,934–2,807 vs. MLLA £1,130 95% CI: £1,046–1,297 vs. BET £329, 95% CI: £242-390, p<.001, Kruskal-Wallis) due to longer procedure duration and greater staff requirement. With regard to the index admission, MLLA was the most expensive due to longer hospital stay (MLLA £13,320, 95% CI: £8,986-18,616 vs. BS £8,714, 95% CI: £6,097-11,973 vs. BET £4,813, 95% CI: £3,529-6,097, p<.001, Kruskal-Wallis). The total cost of the index admission and in-hospital care over the following 12-months remained least for BET (MLLA £26,327, 95% CI: £17,653-30,458 vs. BS £20,401, 95% CI: £12,071-23,926 vs. BET £12,298, 95% CI: £6,961-15,439, p<.001, Kruskal-Wallis).

Conclusion

Over a 12-month time horizon, MLLA and IP BS are more expensive than IP BET in terms of procedural HRe costs and total in-hospital costs. These economic data together with quality of life data from BASIL-2 will inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies within the BASIL-2 cost-utility analysis.

2.5.2 Introduction

Chronic limb threatening ischaemia (CLTI)[13] is an increasing global health and social care problem due to widespread tobacco use and the growing prevalence of diabetes. Patients usually present with complex, multi-level disease, that increasingly involves the infra-popliteal (IP) arteries. The financial consequences of this growing CLTI burden are considerable, especially for low- and middle-income countries (LMIC)[13,14]. In the UK, the total annual direct healthcare cost of caring for CLTI patients has been estimated at £200 million, but this is likely to be a significant underestimate of the true overall financial burden of the disease[124]. In the US, this figure is estimated to be in the range of US$10-20 billion[4]. The annual cost of revascularisation for CLTI in the US has been estimated at US$4.2 billion per year, with an additional US$625 million spent on unplanned re-admissions in the 30-days following intervention[126]. The cost of a CLTI admission in the US has been estimated at around US$23,000[127]. Evidence suggests that all these costs are increasing rapidly[128]. Despite this, there are surprisingly few published studies that have examined the relative costs and cost-effectiveness of the three main primary interventions for CLTI: bypass surgery (BS), best endovascular treatment (BET) and major lower limb amputation (MLLA). This is perhaps because of the difficulty of accurately estimating the true cost of each component of care in the context of a complex patient journey that often involves repeated re-admissions and further procedures, as well as community care, over several years[11,88].

In the UK Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial, the mean overall hospital costs in the 12 months following randomisation were significantly higher after BS (US$34,378) than plain balloon angioplasty (PBA) (US$25,909)[88]. However, due to more hospital admissions and further procedures after PBA, the cost difference reduced to US$5,000 at three years (bypass $45,322 vs. PBA $39,801) and was not significant. Even fewer economic

data are available for CLTI patients undergoing MLLA. One study estimated the in-patient cost at around US$40K based on median stay of 9 days[129]. The only published study of long-term costs following primary MLLA for CLTI suggests it is around $80K over 10 years[130]. However, estimating long-term costs is challenging given the poor overall survival of this group[131].

The UK BASIL-2 trial is randomising CLTI patients between primary IP vein bypass (VB) and best endovascular treatment (BET), which in the UK is predominantly plain balloon angioplasty (PBA), and incorporates a comprehensive cost-utility health economic (HE) analysis[13,14]. The BASIL prospective cohort study (PCS) is running alongside the main trial and comprises all CLTI patients admitted to The Heart of England Foundation Trust, University Hospitals Birmingham (HEFT UHB) vascular unit between July 2014 and September 2018. The aim of the present study is to calculate and compare, over a 12-month time horizon, the costs of primary IP BS, IP BET, and MLLA in patients enrolled in the BASIL PCS in terms of human and hospital-based resource utilisation in order to inform the BASIL-2 HE analyses.

2.5.3 Methods

Patients provided informed, written consent (National Research Ethics Service, Coventry & Warwick, ref: 14/WM/0057). All patients who were admitted to the Heart of England Foundation Trust, University Hospitals Birmingham (HEFT UHB) as an emergency (non-elective, unplanned admission) with CLTI (as defined by the Global Vascular Gudelines[13,14]) were considered. Only patients with significant peripheral arterial disease that would require revascularisation to vessels distal to and including the tibioperoneal trunk were recruited. We compared procedural human resource (HRe) costs and total in-hospital costs for the index admission and over the following 12-months in 60 consecutive patients undergoing primary IP BS (n=20), IP BET (n=20), or MLLA (10 transfemoral and 10 transtibial) for CLTI. Patients were studied clinically for 12 months after discharge from their index admission using

prospectively routinely gathered hospital data. Patients were described in terms of baseline demographics and Wound Ischaemia Foot infection (WIfI) clinical grade to quantify the disease burden of CLTI[29]. Amputation Free Survival and Overall Survival were also estimated for each cohort.

The Heart of England Foundation Trust, University Hospitals Birmingham, UK

Our hospital is the hub of a vascular network that takes referrals and manages patients with vascular disease from three other local, "spoke" institutions. This covers a population base of over 1.2 million patients. At the time of study, the unit was staffed by 6 vascular surgery consultants. There were 24 dedicated in-patient beds and 4 high dependency beds for patients with vascular disease on the vascular ward. The majority of patients with tissue loss secondary to CLTI are admitted as an emergency from either the outpatient clinic, emergency department or surgical assessment unit. We endeavour to adhere to practice guidelines delineating which patients with CLTI should be managed on an in-patient or out-patient basis as prescribed by the Vascular Society of Great Britain and Ireland[113]. We have access to an elective, dedicated vascular operating list for 8 sessions per week (4 full days, 8am to 5pm) and an emergency theatre (twenty-four hours) which is shared between all surgical specialities. At the time of study our hybrid theatre was not yet commissioned. Interventional radiology access was available from Monday to Friday, 8am till 5pm.

Procedural human resource micro-costing

Procedural human resource (HRe) data were collected for each primary intervention from arrival at, to discharge from, the operating theatre or interventional suite. The lead author (MP) attended at the end of each procedure and recorded to the nearest minute the presence of all staff involved. This information was later cross referenced with theatre and interventional

radiology electronic records to ensure accuracy. Staff costs (UK£/hour) were obtained from the Personal Social Services Research Unit (PSSRU) (2018)[132]. Junior medical staff were assumed to be working a 48-hour working week unless otherwise stated.

The Personal Social Services Research Unit (PSSRU), 2018 document "Unit Costs of Health and Social Care[132] delineates the average hourly rates of National Health Service (NHS) staff (dependent on grade). Consultant grade doctors (surgeon / anaesthetist / interventional radiologists) cost the NHS £108 per/hour (p/h). The cost of other hospital-based doctors ranges from £24-£105 p/h depending on grade, based on a 56-hour working week. Hospital based nurses, operating department practitioners (ODP) and radiographers all operate under a banding system in the UK NHS system (from 1 to 9) that attracts pay between £28-£123 p/h.

To calculate median costs, exact hourly rates for the type and grade of personnel present were calculated and multiplied by the time, to the nearest minute, that each individual spent at each phase of a procedure. These costs were then combined for each procedure to give the total HR cost for IP BS, BET and MLLA.

Patient level analysis of in-hospital costs

NHS Index Reference Costs (2014/15)[112] were calculated prospectively from patient level data pertaining to the following:

- index intervention
- index hospital admission: costs for days in hospital were separated into those spent in the ward, high dependency unit (HDU) and intensive care unit (ICU) settings
- further admissions in the 12-months following discharge from the index admission
- further interventions not requiring admission; for example, "day case" BET
- out-patient appointments

- investigations required for diagnosis, treatment and ongoing surveillance
- re-interventions (during the hospital admission and within the following 12-months), any morbidity was described in terms of Clavien-Dindo grade[106].

All costs are reported in Sterling (£) rounded to the nearest whole £.

Statistical Analysis

Variables were tested for normality using the Shapiro-Wilk test, following which comparisons were performed using either the Mann Whitney U or the Kruskal-Wallis tests. Survival data pertaining to amputation free survival (AFS) and overall survival were calculated using the Kaplan-Meier method and groups were compared using the Log Rank statistic. For each Kaplan Meier curve estimate once the number at risk reaches less than 20% of the total cohort results should be interpreted with caution as survival estimates are likely to become less reliable.

The analyses were performed using Jamovi© version 1.0.8.0; a graphical user interface based on the R Statistical Package version 3.6.1©, The R Foundation for Statistical Computing, 2019. Graphical representations were produced using Prism version 8.3.0, GraphPad© 2019.

2.5.4 Results

From the period of 1st June 2014 to the 1st of October 2016, 259 patients were entered into the BASIL-PCS (all-comers with CLTI). From this cohort, 60 patients were selected for analysis (20 IP BS, 20 IP BET, 20 MLLA) which represented 23.2% of the total cohort.

Table 2.5.1 displays the demographics of the populations studied. All three groups were similar in terms of co-morbidity profile, smoking status, obesity, mobility, clinical status, haemodynamic assessment and WIfI clinical grade. More patients who underwent MLLA had undergone previous contralateral limb, above ankle amputation in the past compared to the other two groups.

Procedural details for IP BS and BET can be found in 2.5.2 and 2.5.3 respectively. The majority of bypass patients underwent VB, with only one patient requiring a composite graft (reversed arm vein and PTFE).

All grafts were successfully completed at the time of surgery with no immediate failures. All twenty BS cases were completed under general anaesthesia (GA). One patient in the BS group had a prolonged admission of 127 days and was a clear outlier. Their admission was complicated by significant distal calf wound dehiscence, thrombosis of arteriovenous fistulae for renal dialysis access and urinary tract sepsis requiring admission to a higher level of care. The patient unfortunately died from sepsis during this hospital episode.

Re-interventions were numerous in all cohorts. In the IP BS group, three patients underwent revision surgery to the graft and/or wounds during the index admission. One patient had debridement of an infected groin wound (Clavien-Dindo IIIb). One graft thrombosed within twenty-four hours of surgery and was revised (Clavien-Dindo IIIb).

One patient underwent below knee amputation (BKA) in the same admission following graft failure with no other options for revascularisation. In the 12-months following surgery One patient underwent bilateral above knee amputations (AKA) for non-salvageable CLTI. One patient had an inflow angioplasty above the bypass graft for native artery disease. Another two patients had an outpatient angioplasty of a significant graft stenosis identified by duplex ultrasound surveillance. Two patients had infrainguinal endovascular treatment in the contralateral limb within 12-months of surgery. In total, four patients (20%) underwent repeated revascularisation in the index limb during the study period.

Table 2.5.1 Baseline demographics in patients with infra-popliteal disease analysed in the BASIL-PCS costing study.

MEASURE	Infrapopliteal Bypass (n=20)	Infrapopliteal Best Endovascular Treatment (n=20)	Major Lower Limb Amputation (n=20)	p value
Male sex	15 (75%)	14 (70%)	12 (60%)	.6
Age (mean +/- SD)	74.21 (+/-10.4)	77.5 (+/-10.9)	77.1 (+/- 11.9)	.6
Medical History				
Chronic Kidney Disease	6 (30%)	9 (45%)	8 (40%)	.6
Dialysis dependence	1 (5%)	2 (10%)	2 (10%)	.5
Stroke/TIA	3 (15%)	3 (15%)	4 (20%)	.9
Myocardial Infarction	6 (30%)	4 (20%)	4 (20%)	.7
Angina	5 (25%)	4 (20%)	3 (15%)	.7
CABG	6 (30%)	3 (15%)	2 (10%)	.2
PCI	3 (15%)	3 (15%)	0 (-)	.2
Diabetes	9 (45%)	12 (60%)	11 (55%)	.5
Insulin dependence	3/9 (33.3%)	7/12 ((58.3%)	8/11 (72.7%)	.5
Smoking Status				
Current	7 (35%)	2 (10%)	5 (25%)	.2
Ex	9 (45%)	11 (55%)	7 (35%)	
Never	4 (20%)	7 (35%)	8 (40%)	
Obesity (Body Mass Index >30)	1 (5%)	3 (15%)	3 (15%)	.5
Mobility				
Independent	7 (35%)	3 (15%)	1 (5%)	.2
Walks with aid	12 (60%)	16 (80%)	10 (50%)	

Wheelchair bound	1 (5%)	2 (10%)	7 (35%)	
Bed bound	0 (-)	0 (-)	2 (10%)	
Clinical Status				
Rest pain	15 (75%)	15 (75%)	12 (60%)	.5
Tissue loss	16 (80%)	18 (90%)	17 (85%)	.7
Both	15 (75%)	15 (75%)	9 (45%)	.4
Distribution of tissue loss				
Hallux	10/16 (62.5%)	6/15 (40%)	4/17 (23.5%)	.1
Other toes	1/16 (6.3%)	10/15 (66.6%)	5/17 (29.4%)	.006
Forefoot	1/16 (6.3%)	2/15 (13.3%)	5/17 (29.4%)	.1
Hindfoot	2/16 (12.5%)	0 (-)	3/17 (17.6%)	.2
Ankle	2/16 (12.5%)	2/15 (13.3%)	2/17 (11.8%)	.0
Above ankle	2/16 (12.5%)	3/15 (20%)	6/17 (35.3%)	.2
Medical Therapy				
Aspirin	14 (70%)	11 (55%)	13 (65%)	.9
Clopidogrel	5 (25%)	5 (20%)	6 (30%)	.8
Other antiplatelet agent	4 (20%)	0 (-)	0 (-)	.07
Cholesterol reducing agent	15 (75%)	10 (50%)	14 (70%)	.5
Anti-hypertensive agent	16 (80%)	14 (70%)	14 (70%)	.7
Warfarin	0 (-)	5 (20%)	6 (30%)	.02
Direct Oral Anticoagulant	0 (-)	1 (5%)	0 (-)	.1
Considered Best Medical Therapy	14 (70%)	10 (50%)	13 (65%)	.8

Previous intervention				
Surgical (ipsi)	3 (15%)	5 (25%)	6 (30%)	.2
Endovascular (ipsi)	5 (25%)	2 (10%)	4 (20%)	.9
Minor Amputation (ipsi)	2 (10%)	3 (15%)	2 (10%)	.8
Major Amputation (contra)	0 (-)	1 (5%)	3 (15%)	.02
Ankle Brachial Pressure Index				
Symptomatic leg	2 (10%)	1 (5%)	5 (25%)	
Not done	18 (90%)	19 (95%)	15 (75%)	
Recorded	1 (5%)	6 (30%)	2 (10%)	
Incompressible	7 (35%)	3 (15%)	7 (35%)	
Unrecordable	0.38 (0.42 – 0.54)	0.49 (0.38 – 0.61)	0.48 (0.4 – 0.75)	.5
Median ABPI (IQR)				
WIfI				
WIfI completion	19 (95%)	19 (95%)	17 (85%)	
Total WIfI clinical grade				
Grade 1: Very Low	2/19 (10.5%)	4/19 (21.0%)	0 (-)	.5
Grade 2: Low	6/19 (31.6%)	7/19 (36.8%)	6/17 (35.3%)	
Grade 3: Moderate	7/19 (36.8%)	4/19 (21.0%)	5/17 (29.4%)	
Grade 4: High	4/19 (21.0%)	1/19 (5.3%)	6/17 (35.5%)	

Table 2.5.2 Bypass Treatment Details in those undergoing infra-popliteal bypass in the BASIL-PCS costing study.

n=20		Number
Conduit	Reversed vein	17 (85%)
	Non-reversed vein	3 (15%)
	Leg vein	18 (90%)
	Arm vein	2 (10%)
	Composite	1 (5%)
Proximal anastomosis	Common femoral artery	13 (65%)
	Superficial femoral artery	0 (-)
	Profunda femoris artery	1 (5%)
	Above knee popliteal artery	0 (-)
	Below knee popliteal artery	6 (30%)
Distal anastomosis	Tibioperoneal Trunk	3 (15%)
	Posterior tibial artery 1/3	2 (10%)
	Posterior tibial artery 2/3	2 (10%)
	Posterior tibial artery 3/3	5 (25%)
	Peroneal artery 1/3	2 (10%)
	Peroneal artery 2/3	0 (-)
	Peroneal artery 3/3	1 (5%)
	Anterior tibial artery 1/3	2 (10%)
	Anterior tibial artery 2/3	2 (10%)
	Anterior tibial artery 3/3	1 (5%)
	Dorsalis pedis	0 (-)

Table 2.5.3 Treatment details in those undergoing infra-popliteal endovascular treatment in the BASIL-PCS costing study.

n=20		**Number**
Arteries Treated*	Superficial femoral	4 (20%)
	Above knee popliteal	0 (-)
	Below knee popliteal	6 (30%)
	Tibio-peroneal trunk	3 15(%)
	Posterior tibial	6 (30%)
	Peroneal	7 (35%)
	Anterior tibial	8 (40%)
	Dorsalis pedis	0 (-)
Attempted number of tibial vessel recanalisations	1 vessel	18 (90%)
	2 vessels	2 (10%)
	3 vessels	0 (-)
Type of disease treated	Occlusive	14 (70%)
	Stenotic	5 (25%)
	Combination	1 (5%)
PBA and stent use	PBA only	19 (95%)
	PBA + bail out BMS	0 (-)
	Drug Coated Balloon	1 (5%)
Technical failure		2 (10%)

*Some patients had multiple vessels treated**

All BET cases were performed by a consultant interventional radiologist using local anaesthesia (LA). As is standard practice in the UK, most (90%) had intervention to a single tibial vessel which is usually the least diseased artery. A paclitaxel drug coated balloon (DCB) was used in one case. In two cases it was not possible to cross the target IP lesion. One patient was discharged home for conservative treatment but was re-admitted 2 months later and underwent

a BKA. The patient unfortunately died 1 month following this of sepsis secondary to BKA wound ischaemia. The other patient had rest pain only and had successful SFA angioplasty but reestablishment of inline flow via the anterior tibial was unsuccessful. Treatment of the SFA was sufficient to allow the patients management to continue conservatively until the patient's death in the community 3 years later. No bail out bare metal stents were used in the endovascular cohort. Table 2.5.3 details the vessels treated and technical success rates of the primary interventions only. Subsequent re-interventions were not included.

Foot debridement's were numerous in the BET cohort. Ten debridement's were performed on 8 patients. Eight of these were considered as primary debridement to remove infected or necrotic tissue following successful IP angioplasty. Two patients returned to theatre for further debridement following a failure to heal, both as inpatients. A further patient had an AKA within 12-months in the index limb. Three patients had repeat infrainguinal endovascular treatment in the index limb during the study period (15%).

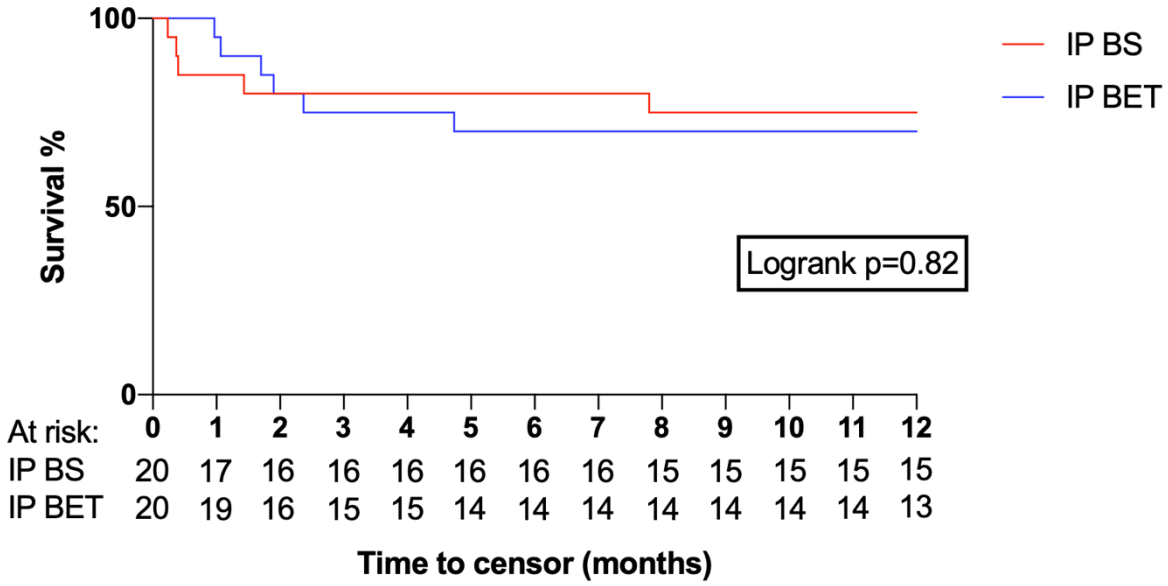
There were no differences in amputation free survival (AFS) at 12-months (IP BS 75% vs. IP BET 65%, HR 0.88, 95% CI: 0.28 – 2.74, Logrank p=0.82) in those undergoing an attempt at revascularisation (Figure 2.5.1).

The majority (85%) of MLLA were performed under GA. Three cases were completed under regional anaesthesia with sedation. There was no significant difference in the total time or HRe procedural costs between those undergoing transfemoral or transtibial amputations (Mann-Whitney U, NS).

Patients undergoing MLLA had a longer median pre-intervention in-patient hospital stay (9 days, IQR 3-21) than those undergoing BS (5 days IQR 1-9) or BET (2 days, IQR 0-7) (Kruskal-Wallis, p=.008). Time to intervention was zero for four patients in the BS and eight patients in

the BET group who attended for a planned, semi-urgent intervention following out-patient assessment and management.

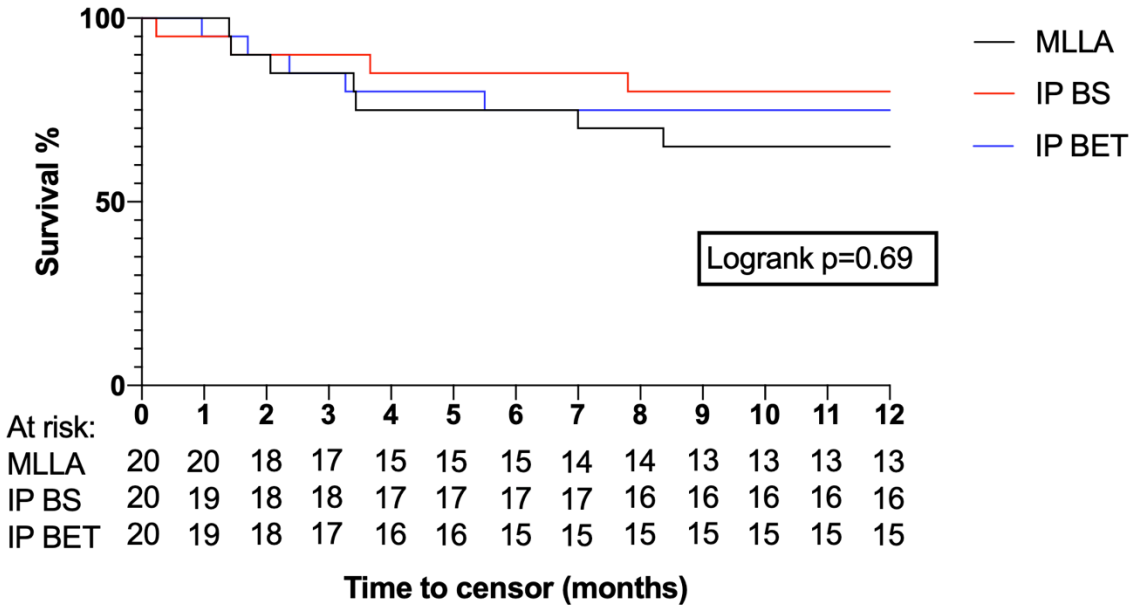
Figure 2.5.1 Amputation Free Survival in 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'.



Two of the BET patients were discharged from hospital on the day of intervention, a further three were discharged the following day. The remaining three patients had prolonged stays, requiring in-patient surgical management of tissue loss. In the MLLA group only one patient was admitted on the day of surgery.

There were no significant differences in overall survival (OS) out to 12-months (Logrank p=0.69, Figure 2.5.2) although OS was somewhat better in those undergoing IP BS (IP BS 80%, IP BET 75%, MLLA 65%).

Figure 2.5.2 Overall Survival in 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'.



Abbreviations: Infra-popliteal (IP), Major Lower Limb Amputation (MLLA), Best Endovascular Treatment (BET), Bypass Surgery (BS).

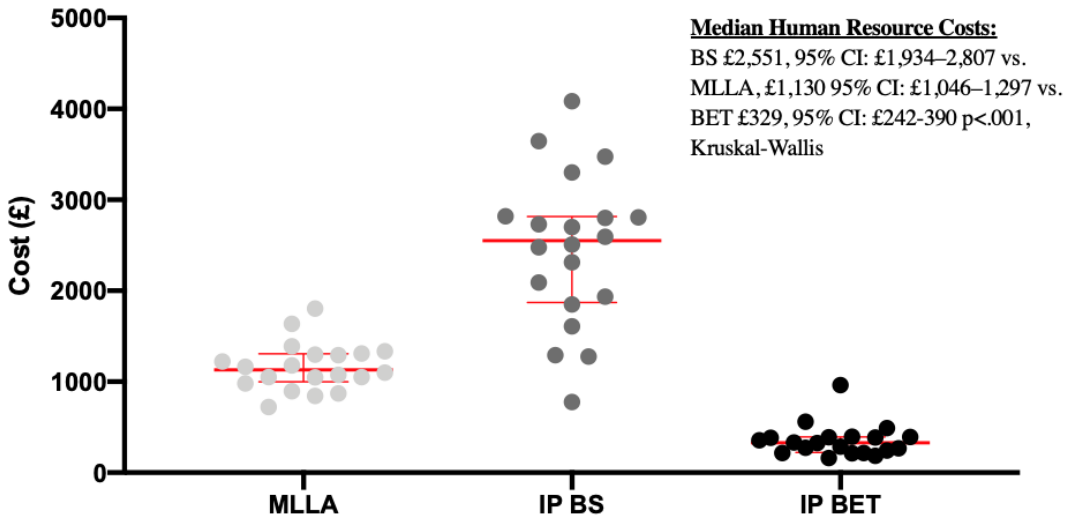
Deaths in the MLLA group were caused by sepsis (2/20), cardiac arrest (2/20), "old age" (1/20), unknown (2/20, community deaths unrecorded in hospital). In the IP BS group mortality was caused by congestive cardiac failure (2/20), mesenteric ischaemia (1/20) and unknown (1/20, community deaths unrecorded in hospital). Finally, in the IP BET group, deaths were due to sepsis (3/20) and unknown (2/20, community deaths unrecorded in hospital).

Procedural HR costs were significantly greater for IP BS than for IP BET or MLLA due to the longer procedural duration and the greater staff requirements, especially where two consultants surgeons were present[132] (Table 2.5.4).

Table 2.5.4 Procedural human resource costs of major lower limb amputation, infra-popliteal bypass surgery and plain balloon angioplasty in the BASIL-PCS costing study.

Median (Inter-quartile range - IQR) cost (UK£) / time (minutes)	***MLLA (n=20)***	***IP BS (n=20)***	***IP PBA (n=20)***	***p value***
Time from arrival in theatre to start of anaesthetic	13 mins (10 - 20)	9 mins (7 - 12)	n/a	
Anaesthetic time	39 mins (25 – 46)	44 mins (29 – 51)	n/a	
Operative time	85 mins (75 – 103)	241 mins (197 – 292)	58 mins (44 – 68)	
Recovery time	48 mins (41 – 93)	83 mins (65 – 127)	n/a	
Total Time	194 mins (180-233)	320 mins (283 – 432)	58 mins (44 – 68)	<.001
Surgeon or interventional radiologist	£134 (£38 – 287)	£798 (£151 – 2158)	£113 (£63 – 333)	<.001
Anaesthetist	£309 (£194 – 529)	£624 (£189 – 1015)	n/a	<.001
Nursing staff	£506 (£339 – 1,014)	£708 (£341 – 1,359)	£144 (£107 - 174)	<.001
Operating Department Practitioner	£134 (£97 – 396)	£220 (£95 – 512)	n/a	.003
Radiographer	n/a	n/a	£53 (£38 - 77)	n/a
Median Total	£1,130 (£720 - 1,820)	£2,551 (£776 - 4,083)	£329 (£161 - 962)	<.001

Figure 2.5.3 Procedural human resource costs in 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'.



Abbreviations: Infra-popliteal (IP), Major Lower Limb Amputation (MLLA), Best Endovascular Treatment (BET), Bypass Surgery (BS).

**Red bars denote median and IQR*

BS was the most intensive in terms of HRe requirement. Four cases (20%) required the presence of two consultant surgeons. Consultant surgeon time is the most expensive at £108/hour, trainee surgeon time is somewhat more variable (£24-105/hour, depending on grade). Having two junior level surgeons in theatre for a case is still more likely to be less expensive than one consultant surgeon, given that very few non-consultant grade surgeons attract the higher tariff pay in the UK. If a single consultant surgeon was operating, they were accompanied by two or

more junior surgeons for the majority of the operating time (13 cases, 65%). A consultant anaesthetist was present in all 20 BS cases.

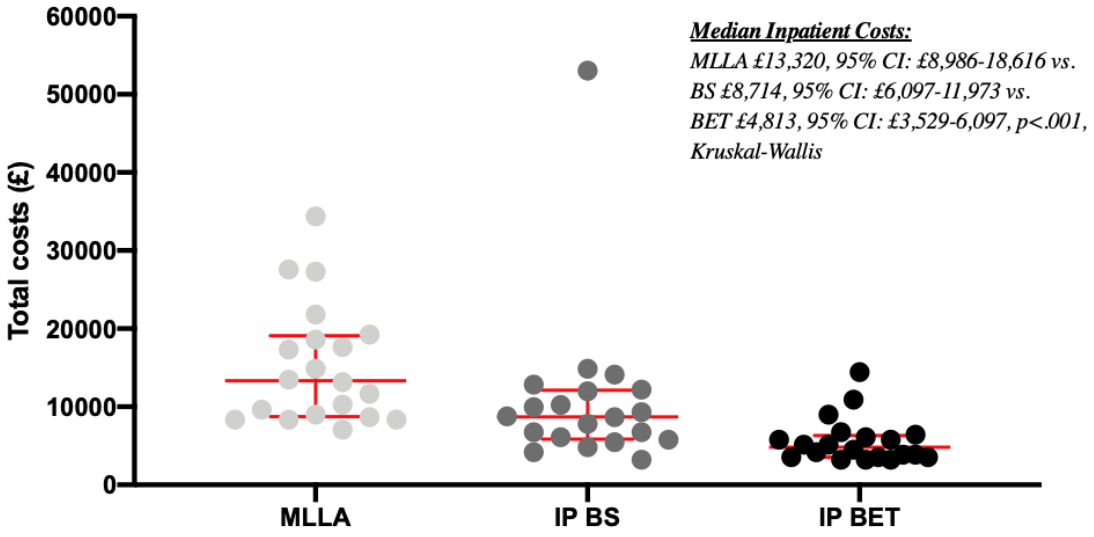
The HR requirements for BET were less variable. All cases were performed by one consultant interventional radiologist. A single training doctor of more junior grade was present for only 35% of cases. MLLA was most commonly performed by surgeons of non-consultant grade. A consultant surgeon was present in only four cases (20%). A consultant anaesthetist was present in theatre for all but one MLLA (95%).

Following their index intervention, patients undergoing BET spent less time in hospital (median 1, IQR 1-5, days) than those who received BS (median 8, IQR 4-17, days) or who required MLLA (median 17, IQR 11-28, days), (Kruskal-Wallis, $p<.001$).

Calculated total hospital costs were significantly greater for MLLA than for either IP BS or IP BET, mainly due to increase length of the index hospital admission (Table 2.5.5**,** Figure 2.5.4).

There were no significant differences re-admissions, days spent in hospital, or out-patient appointments in the 12 months following discharge from the index admission (Table 2.5.5) although total hospital costs still differed significantly (MLLA £26,327, 95% CI: £17,653-30,458 vs. BS £20,401, 95% CI: £12,071-23,926 vs. BET £12,298, 95% CI: £6,961-15,439, $p<.001$, Kruskal-Wallis) (Figure 2.5.5).

Figure 2.5.4 Total costs during index admission in 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'

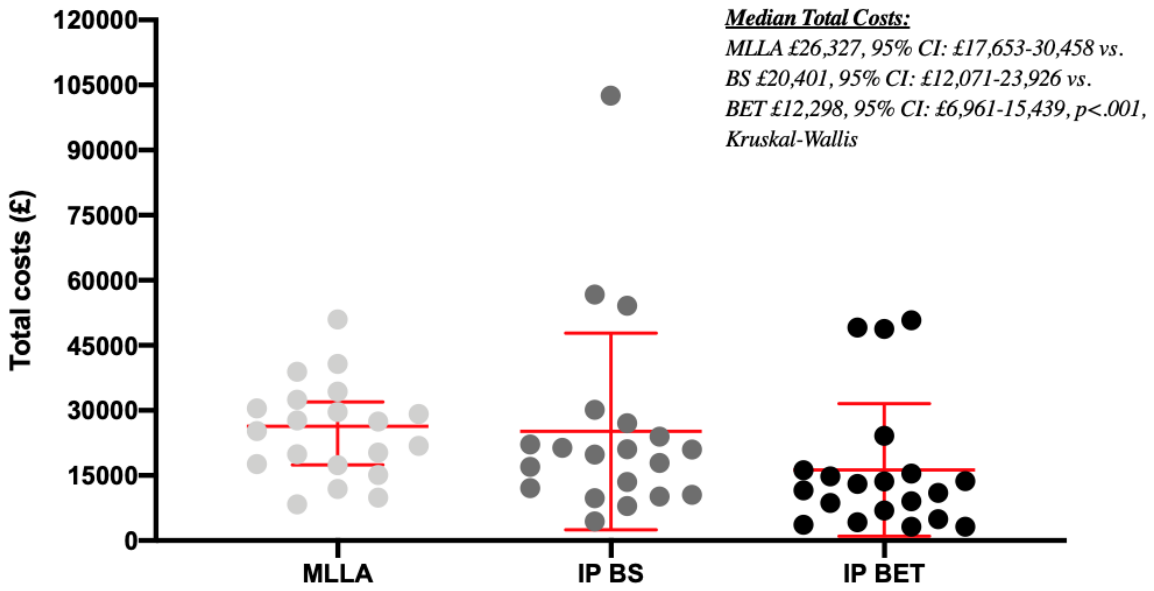


Abbreviations: Infra-popliteal (IP), Major Lower Limb Amputation (MLLA), Best Endovascular Treatment (BET), Bypass Surgery (BS).

**Red bars denote median and IQR*

Although there were no differences in the cost of in-hospital care for MLLA patients compared to those undergoing IP BS this does not include the considerable costs associated with ongoing community care, rehabilitation, and limb fitting.

Figure 2.5.5 Total costs hospital cost from index admission to 12 months after discharge for index admission in 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'.



Abbreviations: Infra-popliteal (IP), Major Lower Limb Amputation (MLLA), Best Endovascular Treatment (BET), Bypass Surgery (BS).

**Red bars denote median and IQR*

Table 2.5.5 Comparison of resource usage and costs 'Procedural and 12 month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischaemia'.

Median (IQR)	**MLLA (n=20)**	**BS (n=20)**	**BET (n=20)**	**p value**
Days from admission to intervention	9 days (3 – 19)	5 days (1 – 8)	2 days (0 – 6)	<.001
Days spent in hospital following intervention	17 days (11 - 28)	8 days (4 – 7)	1 day (1 – 5)	<.001
Inpatient bed days during index admission	30 days (18 - 45)	11 days (7 – 23)	5 days (1 - 9)	<.001
Index admission costs	£13,320 (£8,745 – 19,098)	£8,714 (£5,856 - 12,140)	£4,813 (£3,529 - 6,338)	<.001
Hospital admissions following index admissions	1 (0 – 2)	1.5 (0.75 – 2)	1 (0 – 2)	NS
Days spent in hospital in the 12 months following discharge from the index admission	7 (0 – 20)	15 (2.5 – 24.3)	7.5 (0 – 13.3)	NS
Outpatient appointments following discharge from	2 (0 – 6.25)	4 (2.5 – 7.25)	2 (1 – 3.25)	NS

the index admission				
Total costs over 12-months (from index admission to 12 months after discharge from index admission)	£26,327 (£17,447 - 31,973)	£20,401 (£10,903 - 26,266)	£12,298 (£5,429 - 16,029)	<.001

2.5.5 Discussion

The present study has found that, over a 12-month time horizon, IP BS is more expensive than IP BET or MLLA in terms of procedural HR costs due the greater requirements for time and staff. This accords with other published data[18]. This was largely due to the presence of more consultant grade staff (at least 2, 1 surgeon, 1 anaesthetist) and assistants required for BS. The range of HR costs of BS was greater than for the other two interventions, probably due to variations in conduit use (arm vein for example) and the location of the distal anastomosis. BS by nature is less predictable and each case presents its own unique challenges. MLLA is much more predictable operation.

Although from a technical perspective, BET can also be unpredictable, the HRe costs were more tightly grouped. All cases were performed under LA, by a single consultant interventional radiologist without the requirement of an anaesthetist. Following manual compression, or use of closure device, and adequate haemostasis patients returned directly to the vascular ward without the need for the use of a recovery area. These factors largely explain the lower HR costs for BET.

BET was also the least expensive intervention in terms of hospital costs, which is perhaps unsurprising given that BET is generally quicker to perform and requires less recovery in-hospital. Eight patients (8/20, 40%) underwent planned, semi-elective therapy which was a much higher proportion than those undergoing MLLA or BS.

Patients undergoing MLLA tended to have a prolonged index admission. Moreover, timely discharge to “step-down” facilities for on-going care would have reduced the hospital costs associated with the index admission. Also, the lead time from admission to MLLA was

relatively long (9 days median) largely due to prior attempts at limb salvage, debridement or drainage of sepsis; or an initial unwillingness on the part of the patient to accept MLLA.

The index hospital admission costs for all three procedures are tightly grouped (Figure 2.5.4) except one outlier who underwent BS. This patient had a protracted stay in hospital following a femoro-peroneal bypass with complicated wound sepsis (groin) that required debridement, negative pressure therapy and an intensive care stay with acute renal failure.

Ongoing hospital-based care in terms of outpatient appointments, re-admissions and days spent in hospital in the 12-months following discharge after the index intervention were non-significantly different. Total costs (index admission plus ongoing hospital-based care over 12 months) were greatest for those undergoing MLLA and BS. This was due to the relatively expensive index episodes.

We opted not to individually cost for devices and equipment based on the complexities of health care purchasing in the UK National Health Service (NHS). Each individual NHS hospital trust has contracts with different device manufacturers that are often based on the volume and frequency of use as well as consignment stock. Each hospital trust has its own financial agreement with manufacturers. The financial details of these agreements are usually not disclosed. For these reasons, the cost of devices in our unit may be very different to other hospitals with different device preference and frequencies of use.

There were no pedal bypasses in the IP BS cohort. In recent years, our colleagues have increasingly adopted an endovascular first revascularisation strategy in patients presenting with CLTI. In period from which the current patients were selected (June 2014 to September 2016) 259 patients were admitted to HEFT UHB with CLTI as an emergency (for in-patient care).

During this time period, only one popliteal to pedal (dorsalis pedis artery) bypass was performed.

Patients undergoing IP BS had longer delays to treatment than those undergoing IP BET. This is likely to be the case most, if not all, UK vascular units. Patient who require IP BS often require a much more extensive pre-procedural workup in terms of anaesthetic review, further investigations to delineate fitness for treatment and often more investigations (vein map, computed-tomography angiography, arterial duplex, digital subtraction angiography) compared to those undergoing IP BET. In addition, it can be difficult to access sufficient operating theatre time for often prolonged emergency surgery. Again, this is a common problem right across the NHS.

Costs need to be weighed against patient outcomes and, in particular, data on health-related quality of life, so that a cost-utility analysis can be used to compare cost-effectiveness of different treatment strategies. In the UK, The National Institute of Health and Care Excellence (NICE) use cost per quality of life adjust year (QALY) as a marker of value, with a current willingness to pay threshold set nationally at £20,000 per QALY[90]. A recent systematic review into the cost-effectiveness of a BET versus BS strategy for patients with CLTI secondary to infrainguinal disease reported that BASIL-1 was the only RCT for which health economic data were available[133]. The Veterans Association study group concluded that significant, modern evidence was severely lacking to inform healthcare providers and that future ongoing RCT's are required to provide this (BASIL-2[12], BEST-CLI[33]).

Human resource costs are notoriously difficult to estimate, the PSSRU[132] document that we used to calculate such costs is a standardised format based on average basic salaries. This does not include any uplifts in pay for extra activity, such as teaching or managerial roles, or service

awards. Although PSSRU HR have been costs may have been an underestimate, it is the best data source available.

The current micro-costing analysis does not present cost effectiveness. In the UK, cost effectiveness is measured as a 'cost per QALY' or an incremental cost effectiveness ratio (ICER). This is calculated using not only costs (similar to this chapter) but also quality of life measures (usually EQ 5D 5L). Unfortunately, consent for data collection in this study, and in the BASIL-PCS did not include the prospective collection of HRQoL data, therefore ICERs for either revascularisation strategy could not be calculated. These data however are still unique and will help to provide information when calculating ICERs in the BASIL-2 trial when it completes follow up in the coming months.

2.5.6 Limitations

The current study estimates costs over a relatively short, 12-month, time horizon and so does not include the costs of later re-admissions and re-interventions, rehabilitation, limb fitting and on-going social care, either at home or in a residential institution.

Rehabilitation services are completely separate from the hospital. Following discharge from hospital, patients with MLLA are usually seen in the outpatient's department at around 6 weeks to ensure adequate wound healing. If there are no concerns, they are usually discharged from the vascular service.

Although NHS hospitals are likely to have varying salary and estates costs, we cannot comment formally on the generalisability of our data to other UK vascular units.

Bearing this in mind, and dearth of evidence in the literature regarding the true costs of managing CLTI, further large, multicentre studies are clearly required.

2.5.7 Conclusions

In conclusion, over a 12-month horizon, in terms of calculated procedural HRe and in-hospital costs, both IP VB and MLLA are more expensive than IP PBA. Although out to 12 months after discharge from the index admission, the difference in overall hospital costs reduces, it remains significant. These economic data together with QALY data from BASIL-2 will help inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies.

3 DISCUSSION

Each individual subsection has already been discussed at length at the end of each study in sections 2.1 to 2.5. Here the discussion will focus more on general limitations of the Thesis methodology as a whole as well as future work that is required to improve outcomes in this challenging patient group. Finally, BASIL-2 has recently completed recruitment, its importance cannot be understated in terms of proving clinicians with an evidence base in which to practice within when treating patients with IP disease.

3.1 LIMITATIONS OF THESIS METHODOLOGY

In section 2.1 a post-hoc analysis was performed on a subgroup of patients with CLTI secondary to IP disease in the BASIL-1 trial. The study was not powered to demonstrate significant differences in AFS between the two strategies. Results from this subgroup analysis must therefore be interpreted with caution. However, it is important to note that patients in these groups were randomised to a specific treatment rather than selected, which increases the validity of the findings. It seemed an appropriate analysis to begin the investigation into the management of CLTI secondary to IP disease given the general lack of high quality, publicly funded data available in the literature at the time of the analysis. The subgroup analysis was well received by the vascular community and was published in the *European Journal of Vascular and Endovascular Surgery* and presented at the Charing Cross Symposium in 2017.

Sections 2.2 and 2.3 represent retrospective analyses of prospectively gathered data, clearly such analyses are prone to a variety of bias (primarily selection). The impact of which was kept to a minimum by using appropriate statistical methods as well as cautiously interpreting the data given the inherent differences observed between groups. The main drawbacks of the data studied in these sections were a lack of objective ways of characterising the patients and their

disease presentations (WIfI, PEDIS, GLASS). It was not possible to gather such data mainly due to a lack of haemodynamic measurements. Like all retrospective studies the results are essentially at the mercy of data quality from previous data entry. Without haemodynamic data it is impossible to calculate WIfI scores and therefore the PLAn principles laid out by the GVG committee. Such information would have made comparisons between the groups in these sections more meaningful. Sections 2.2 and 2.3 have both been published in the *Journal of Vascular and Endovascular Surgery*.

The BASIL-PCS was an attempt to quantify the burden of CLTI in East Birmingham (section 2.4). The study methodology aimed to correct the drawbacks of the retrospective methodology used in the previous sections by accurately documenting objective haemodynamic and wound scoring indices to properly characterise disease presentations. The ascertainment rate of haemodynamic and wound scoring systems such as ABPI, WIfI and PEDIS was acceptable. It was not possible to have a '24/7' presence in the hospital to ensure 100% data completion. Prospective cohort studies are resource intensive and require a lot of manpower to increase data capture. Most of the data was collected by the lead author (MP) except during times of leave. One major flaw in the study is the generalisability of the findings to other vascular units in the UK and in fact, the rest of the world. In an ideal setting, a larger multi-centre prospective cohort study would have increased the external validity of the findings. Importantly, the PCS demonstrated the ongoing need for high quality, unbiased publicly funded data to guide the management of this challenging patient group.

Statistical advice was sought from the Birmingham Clinical Trials Unit (BCTU) from two authors (Mrs Smitaa Patel and Professor Jon Deeks) for the analyses performed in section 2.1 and 2.2. Following guidance on these first two sections the rest of the analyses were performed independently by MP. Advice was sought from a qualified health economist (Dr Lazaros

Andronis, BCTU) for planning of the final section 2.5. Statistical analysis again was performed independently by MP.

The reporting of Kaplan Meier statistics has been debated for some years since the inception of the method in 1958[134]. Pocock et al published some good practice guidance in 'The Lancet' in 2002[135] which suggest that survival curve data that is presented when less than 10-20% of the original cohort at risk is prone to unreliable estimates (a cut off of 20% was chosen for the methodology of this thesis to provide conservative estimates given the non-randomised, under-powered nature of some of the data). Despite this however, the calculation of the Logrank statistic when making comparisons between survival curves includes all of the data in the time to event analysis. It appears generally accepted that data to the right side of the Kaplan-Meier estimate should be interpreted with caution particularly in observational studies[136]. In this thesis the majority of data sets were of modest size, therefore the 'number at risk' reported in most Kaplan Meier curve estimates were low in the later years of follow up. It is therefore difficult to make any strong conclusions regarding long-term follow up data in these cohorts.

FUTURE WORK

3.2 WHY DO WE NEED FURTHER EVIDENCE TO MANAGE PATIENTS WITH CHRONIC LIMB THREATENING ISCHAEMIA SECONDARY TO INFRA-POPLITEAL DISEASE?

In contemporary surgical practice the role of evidence-based medicine (EBM) is widely accepted by vascular surgeons (VS) and interventional radiologists (IR) alike. The General Medical Council (GMC) in the United Kingdom states that clinicians should "provide effective treatments based on the best available evidence" in the "Good Medical Practice" guide[137]. In

2012, NICE made the investigation of revascularisation strategies for those with IP disease a priority research recommendation[22]. In a similar fashion a stakeholder group selected by the Society for Vascular Surgery (SVS) in United States concluded that quality research reviewing "the effectiveness of initial open versus endovascular infrainguinal revascularisation for critical limb ischaemia" was lacking and was therefore given high priority for future research after a systematic scoring exercise[105]. In 2021, these calls for higher quality evidence have still not been answered.

Generally, publications have been multiplying, particularly industry funded data surrounding the use of drug elution and stenting. Despite this, good quality evidence in terms of robust randomised control trials or meta-analyses, are few in number, particularly when relating to comparisons with more established revascularisation strategies such as plain balloon angioplasty (PBA) and open, vein bypass surgery.

The rapid invent of multiple endovascular therapies and techniques have, in some ways, outstripped the ability of VS and IR to perform meaningful, long term evaluation. Outcomes are usually focused on technical endpoints such as patency, rather than hard clinical outcomes such as AFS, HRQoL and healing of ischaemic wounds and rarely show benefit over more established, much cheaper techniques[28] which still provide suboptimal procedural and short term clinical outcomes[75].

3.2.1 Why are there so few Randomised Controlled Trials to address a lack of evidence?

RCT's in CLTI due to IP historically have been difficult to undertake. The BASIL-1 trial is still the key level 1 evidence available currently in the literature when comparing open surgical bypass and angioplasty as a 'first' revascularisation strategy. The trial however was not powered statistically to show a subgroup effect in such patients (roughly 25% of patients had

significant infrapopliteal disease)[11]. RCTs remain the gold standard of providing level 1 evidence to clinicians, with high levels of internal validity, detailed prospective analyses with significant financial pressures from sponsors to maintain accurate data and participant recruitment. Conversely, they can be difficult to set up, recruitment can be difficult, particularly when reviewing subsets of patients with IP disease and above all, are expensive. Current completed RCTs aim to bridge current gaps in knowledge (BASIL-2[12], BEST-CLI[33]) but are still some months, if not years away from reporting their outcomes at the time of writing.

The IDEAL (Idea Development Exploration, Assessment, Long Term Study) group in 2013 recognised that surgical techniques and devices follow a development pathway that is very different from pharmaceutical products. The group recognised that the evidence for much of surgical practice was poor, and that high-quality evidence in terms of RCTs and systematic reviews were small in number[138]. The group also recognised that surgical and interventional trials were not as simple to conduct as success is often due to variables such as operator skill and judgement as well as patient complexity[139]. Based on these factors the group developed a framework for evaluating surgical innovation, the stages of which are summarised in Table 3.2.1

Surgical procedures have many variables which may influence the outcome of a trial such as operator skill, patient complexity, form of anaesthesia and the use of best medical therapy. The IDEAL group identified three main difficulties that act as barriers when evaluating surgical procedures and/or techniques[89].

1. A clear definition of the intervention
2. Treatment preferences of the surgeon
3. Treatment preferences of the patients

Table 3.2.1 The IDEAL Framework.

Stage	Aims & Objectives
1: Idea	Proof of concept, first in man study
2a: Development	Discover optimal technique design/patient group, safety/efficacy
2b: Exploration	Outcomes of widespread use, equipoise for trial question, efficacy
3: Assessment	Comparison with standards of care, effectiveness
4: Long Term Study	Long term effects and outcomes of the procedure, quality assurance

Such issues could act as a deterrent to randomisation into much needed CLTI trials due to IP disease. Many VS and IR have adopted an endovascular first revascularisation strategy and lack clinical equipoise between open surgical and endovascular treatments. Factors that may influence this include; decreased access to the operating theatre, diminishing operative skills to perform an effective surgical bypass, an increasingly comorbid western population and negative attitudes toward a perceived higher risk of performing open surgery. These difficulties should not deter from performing high quality RCT's in areas where clinical evidence is lacking[89].

3.2.2 Can registry data provide meaningful conclusions?

In the absence of high-quality level 1a evidence, well timed and delivered observational and registry data can provide clinicians with useful information. In particular such studies can act as a precursor to grant application for a RCT or provide long term safety and effectiveness data. However, such studies should be conducted with as many features of an RCT as possible [140]. Table 3.2.2 details the IDEAL features of an effective observational study[141].

To access multi-institutional data, two sources of information are readily available; administrative data or clinical registry data. Administrative data (such as the hospital episode statistics (HES) http://digital.nhs.uk/hesdata set in the UK), has been used by health care providers to reimburse for inpatient hospital episodes. Such systems allow for the indirect collection of clinical information, however, rely solely on the accuracy of clinical coding, which has led to inadequate reporting of surgical outcomes[142]. Clinical registries offer users the ability to record more specific data relating to a specific procedure or intervention. This can be a large national registry such as the National Vascular Registry (NVR) or a smaller local registry or prospective cohort study initiated by individual centres. Accuracy again is difficult to obtain, consecutive episodes need to be recorded without missing cases, which is resource intensive in terms of manpower[143].

In the UK, the NVR is currently maintained, audited and outcomes periodically published through the Vascular Services Quality Improvement Programme (VSQIP). The most recent NVR report in 2020 has recorded national case ascertainment of bypass and endovascular treatments since January 2017 until December 2020, reporting on short term outcomes[59]. This is a major problem with the NVR in its current format, in that 'success' is judged on 30-day outcomes alone which arguably misses the most important CLTI outcome data (wound healing, freedom from rest pain, limb salvage). Making direct comparisons between bypass surgery and angioplasty is extremely difficult, given the diametric figures quoted for case ascertainment when compared with expected HES data between the two treatment modalities (approximately 90% case ascertainment for bypass procedures versus 47% for endovascular treatments).

Table 3.2.2 IDEAL features of an effective observational study.

IDEAL recommendations for exploratory observational studies
Prospective data collection with a protocol
Range of outcomes collected using standardised definitions
Important risk factors and patient variations should be explored
Record surgeon experience
The effect of skill differences and learning should be assessed by appropriate data analysis
Studies should be designed with a definitive evaluation (RCT) in mind
IDEAL recommendations for assessment observational studies
Use a quasi-experimental study design; protocol driven controlled studies with standardised eligibility and prospective data collection
Possible designs include non-randomised trials and interrupted time series
Key patient and centre characteristics likely to confound should be considered before conducting analysis and adjusted for/matched.

This report highlights important issues with such prospective, observational data in that case ascertainment is key. It is very difficult to draw any meaningful conclusions from the data due to the poor reporting rates of endovascular procedures, lack of detail regarding disease segments and severity of peripheral arterial disease.

Whilst small observational studies are numerous in the IP literature there is still paucity in high quality evidence to determine a “first” treatment strategy. The use of new endovascular technology is on the increase despite a lack of significant evidence.

The clinical and cost effectiveness of which can only be determined by a combination of RCTs and good, well maintained prospective cohort studies and registries to provide clinicians with longer term outcome data. Current economic and political challenges should not deter VS and IR from offering patients important clinical studies such as the (BASIL-2 and BEST-CLI trials) in specialisation of vascular surgery where there is still a large grey area of intellectual and clinical equipoise.

4 CONCLUSIONS

This Thesis has provided much needed data to support the ongoing efforts to provide clinical and cost-effectiveness data to guide clinicians in decision making for patients with CLTI secondary to IP disease. The data in this Thesis demonstrates that IP vein bypass is probably the most efficacious treatment in the long-term in patients who have a venous conduit and are fit enough to withstand an open surgical procedure.

Outcomes from IP PBA have not improved since the BASIL-1 trial in our unit, despite a perceived improvement in endovascular technology in terms of access, treatment and closure. This may represent a cohort of patients in which any form of revascularisation is futile but were a 'nothing to lose' strategy is applied as a first treatment strategy instead of primary MLLA. The CLTI population appears to be aging, becoming less fit and hospitals are busier than ever which may encourage an endovascular first treatment strategy in this patient group.

Outcomes in those with CLTI in the BASIL-PCS were extremely poor, in that AFS and OS at 5-years were significantly worse than most cancers. This may be a representation of a changing population with more comorbidity, enhancing age and poorer socioeconomic circumstances. Patients sometimes undergo multiple endovascular procedures to achieve limb salvage in a short period of time only to succumb to other illness or comorbidity, if this is to be seen as a success there is a requirement for research that addresses patient centred outcomes such as quality of life and freedom from tissue loss or rest pain. Current literature focuses primarily on technical outcomes or 'hard' clinical endpoints such as amputation and death which are seemingly inappropriate in the patient profile, we are now treating in 2021.

The data in This Thesis helped to stimulate debate and reinforced the clinical equipoise that exists when treating patients with CLTI secondary to IP disease. The published studies and BASIL-PCS will help to inform generalisability and the cost effectiveness analysis in the BASIL-2 trial which is due to report in 2022.

All of the above factors highlight the importance of the BASIL-2, BASIL-3 and BEST-CLI trials in providing much needed data regarding wound healing, HRQoL and cost effectiveness to aid health care purchasers, clinicians and patients in decision making regarding the treatment of CLTI.

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APPENDIX 1: BASIL-2 Trial Protocol

Trials



Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial

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DOI 10.1186/s13063-015-1114-2

Popplewell et al. Trials (2016) 17:11
DOI 10.1186/s13063-015-1114-2

Trials

STUDY PROTOCOL Open Access

Bypass versus angio plasty in severe ischaemia of the leg - 2 (BASIL-2) trial: study protocol for a randomised controlled trial

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Abstract

Background: Severe limb ischaemia is defined by ischaemic rest/night pain, tissue loss, or both, secondary to arterial insufficiency and is increasingly caused by infra-popliteal (below the knee) disease, mainly as a result of the increasing worldwide prevalence of diabetes. Currently, it is unknown whether vein bypass surgery or the best endovascular treatment (angioplasty or stenting) represents the optimal revascularisation strategy in terms of amputation-free survival, overall survival, relief of symptoms, quality of life and cost-effective use of health care resources.

Methods/Design: The Bypass vs. Angioplasty in Severe Ischaemia of the Leg - 2 Trial is a UK National Institute of Health Research, Health Technology Assessment funded, multi-centre randomised controlled trial that compares, at the point of clinical equipoise, the clinical and cost-effectiveness of a 'vein bypass first' and a 'best endovascular treatment first' revascularisation strategy for severe limb ischaemia due to infra-popliteal disease. The primary clinical outcome is amputation-free survival defined as the time to major (above the ankle) amputation of the trial limb or death from any cause. The primary outcome for the cost-effectiveness analysis is cost per quality-adjusted life year. Secondary outcomes include overall survival, quality of life, in-hospital mortality and morbidity, repeat and crossover interventions, healing of tissue loss and haemodynamic changes following revascularisation. Sample size is estimated at 600 patients. An economic evaluation will be conducted from the perspective of the National Health Service and comprise a 'within-study' analysis, based on prospectively collected trial data and a 'model-based' analysis, which will extrapolate and compare costs and effects beyond the study follow-up period.

Discussion: The BASIL-2 trial is designed to be pragmatic and represent current practice within the United Kingdom. Patients with severe limb ischaemia can only be randomised into the trial where clinical equipose exists. The advent of hybrid operating procedures should not be a barrier to randomisation, should a patient require inflow correction prior to tibial revascularisation.

Trial registration: ISRCTN:27728689 Date of registration: 12 May 2014.

Keywords: Severe limb ischaemia, Critical limb ischaemia, Bypass surgery, Endovascular treatment, Angioplasty, Stent, Diabetes, Amputation

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Background

As a result of smoking, diabetes, high blood pressure, high cholesterol, kidney failure, and old age, some people develop atherosclerosis (*aka* 'hardening of the arteries) in their legs.

This atherosclerosis narrows and eventually blocks their arteries, thereby reducing the blood supply to their legs and feet: a condition termed 'ischaemia'.

Advanced cases are known as 'severe limb ischaemia' and cause one or both of the following problems:

1) Injuries to the foot fail to heal, allowing infection to enter the tissues, resulting in the development of ulceration, and even gangrene.
2) Severe constant pain in the foot, which is often worse at night and disturbs the sleep.

In the developed world, the incidence of critical or severe limb ischaemia is estimated at 500 to 1,000 per million population [1].

The number of people affected by severe limb ischaemia is increasing worldwide as a result of the ageing population, the increase in diabetes, and the continuing high rates of smoking [2].

In people with severe limb ischaemia, if the blood supply to the leg is not restored (revascularisation), then the risks of amputation and death are high. In the UK, approximately 5,000 to 6,000 amputations are performed each year, the great majority for severe limb ischaemia [3].

1) In addition to best medical therapy (comprising anti-platelet and lipid modifying agents, optimal diabetic control, analgesia, and foot and wound care), which all patients should receive as indicated, severe limb ischaemia can be managed by means of the following:
2) Primary amputation, when the limb is beyond salvage and/or the patient is unfit/unwilling/unable to undergo revascularisation.
3) Surgical revascularisation, which is usually undertaken by means of a bypass fashioned using an autologous vein and/or endarterectomy.
4) Endovascular revascularisation, which is a 'keyhole' procedures performed through the groin under local anaesthetic and using balloons and stents to force/hold open the arteries.

The current evidence base underpinning the treatment of severe limb ischaemia is extremely poor with very few randomised clinical trials [4] and no available systematic reviews or meta-analysis.

The National Institute of Health and Care Excellence clinical guideline (CG) 147 on Peripheral Arterial Disease recommended that a randomised controlled trial be undertaken to answer the following question which BASIL-2 aims to answer: namely, 'What is the clinical and cost effectiveness of a 'bypass surgery first' strategy compared with an 'angioplasty first' strategy for treating people with critical limb ischaemia caused by disease of the infra-geniculate (below the knee) arteries?' [5]

Aims

The original BASIL-1 trial, on which BASIL-2 is based, randomised 452 patients with severe limb ischaemia, mainly due to femoro-popliteal disease (in the thigh), to either an angioplasty first or a bypass surgery first revascularisation strategy [4]. The Bypass vs. Angioplasty in Severe Ischaemia of the Leg - 2 (BASIL-2) Trial is a UK National Institute of Health Research, Health Technology Assessment funded, multi-centre randomised controlled trial (http://www.nets.nihr.ac.uk/projects/hta/123545) that will now compare, at the point of clinical equipoise, the clinical and cost-effectiveness of a 'vein bypass first' with a 'best endovascular treatment first' revascularisation strategy for severe limb ischaemia due to infra-popliteal (below the knee) disease (Fig. 1). BASIL-2 includes an internal pilot phase and economic analysis. The primary clinical outcome is amputation free survival defined as the time to major (above the ankle) amputation of the index (trial) limb or death from any cause, whichever comes first. The primary outcome for the cost-effectiveness analysis will be cost per quality-adjusted life year. Secondary outcome measures are shown in Table 1.

Methods

Ethics

Ethical approval was gained via the National Research Ethics Service, West Midlands, UK (Coventry and Warwick) on 3 March 2014 (reference 14/WM/0057). Each patient will provide fully informed, written consent prior to randomisation.

Eligibility

All patients with severe limb ischaemia referred to vascular units within participating NHS Trusts can be considered. To be eligible for randomisation, patients must have adequate inflow to support infra-popliteal intervention, an anticipated life expectancy greater than 6 months, capacity to consent, and be able to speak English where translation facilities are unavailable (Table 2). Previous intervention to the trial leg is not an exclusion criterion.

Potentially eligible patients will be discussed at a formally minuted multi-disciplinary meeting comprising vascular surgeons and interventional radiologists. If the patient is deemed suitable for both treatment arms and there is clinical equipoise as to which revascularisation strategy is most appropriate, they will be invited to enter the trial.

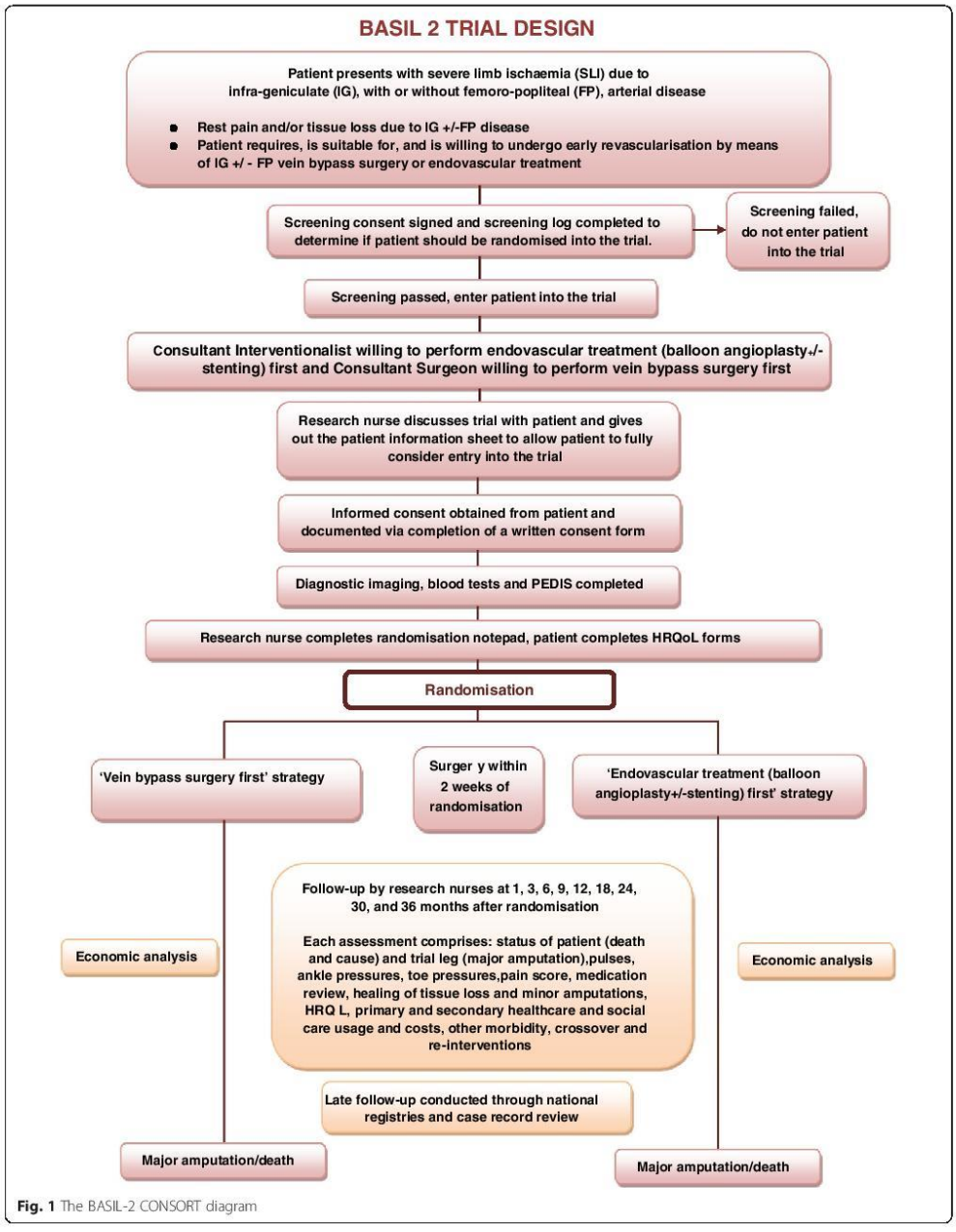


Fig. 1 The BASIL-2 CONSORT diagram

Table 1 BASIL-2 secondary outcomes

Overall survival
In-hospital and 30-day morbidity and mortality
Major adverse limb event – amputation (transtibial and above) or any major vascular re-intervention (thrombectomy, thrombolysis, balloon angioplasty, stenting or surgery)
Major adverse cardiovascular event – (severe limb ischaemia and amputation affecting the contralateral limb, acute coronary syndrome, or stroke)
Relief of ischaemic pain (visual analogue scale and medication usage)
Psychological morbidity (Hospital Anxiety and Deprivation Score)
Quality of life using generic (European Quality of life 5 level questionnaire, Short Form-12, ICEpop CAPability for older people and disease specific Vascular Quality of Life) tools
Re- and cross-over intervention rates
Healing of tissue loss (ulcers, gangrene) of presumed arterial aetiology as assessed by the Perfusion Extent Depth Infection Sensation [6] and Wound Ischaemia Foot Infection [7] scoring and classification systems
Extent and healing of minor (toe and forefoot) amputations (also using the above wound scoring systems)
Haemodynamic changes: absolute ankle and toe pressure, (ankle brachial pressure index and toe brachial pressure index).

Randomisation

Blinding of the clinician and patient in this trial is not possible due to the completely different natures of the treatments allocated.

Randomisation is provided by a web-based third party service with a telephone option if required. The first 30 patients shall be allocated randomly, subsequently four out of every five patients are minimised, with 1 in 5 patients randomly allocated using random block without regular spacing. The following minimisation variables will be used:

- age (≤60, 61 to 70, 71 to 80, > 80 years),
- sex (male or female),
- diabetes mellitus and chronic kidney disease* (diabetes mellitus, chronic kidney disease, both or neither, where chronic kidney disease is defined as stage 3 or worse, based on estimated glomerular filtration rate of < 60 (ml/min/1.73 m^2), and
- severity of clinical presentation (rest/night pain only, tissue loss only, or both).

Baseline assessment

After randomisation patients undergo a baseline assessment comprising the following:

1. Patient history including risk factors for vascular disease, co-morbidities, previous arterial interventions to either leg, amputations and coronary interventions.
2. Physical examination including assessment of functional status, peripheral pulses, ankle-brachial pressure index and toe-brachial pressure index.
3. Review of investigations including imaging and results of blood tests.
4. Foot assessment using the Wound Ischaemia Foot Infection (WIFI) [6] and Perfusion Extent Depth Ischaemia Sensation (PEDIS) [7].
5. Assessment of Quality of Life using the Visual Analogue Scale, European Quality of life 5 level score, Short Form-12, ICEpop Capability for Older people, Vascular Quality of life, and Hospital Anxiety and Depression Scale.

The allocated intervention should be performed within 14 days where clinically and logistically possible.

Trial interventions

Vein bypass will be performed using standard anaesthetic and surgical techniques. The type of vein used, and the location of the proximal and distal anastomoses, will be recorded. Best endovascular treatment will usually be performed under local anaesthetic via the common femoral artery. Success of vein bypass and best endovascular treatment will be assessed by pulse status, completion angiography and haemodynamic measures such as ankle brachial pressure index.

Table 2 BASIL-2 inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Have severe limb ischaemia due to infra-popliteal, +/− femoropopliteal disease	Have an anticipated life expectancy of < 6 months
Be judged by responsible clinicians (consultant vascular surgeon, interventional radiologist, and diabetologists) working as part of a multi-disciplinary team to require early revascularisation in addition to best medical therapy, foot and wound care.	Are unable to provide consent due to incapacity
Have adequate inflow to support the randomised infra-popliteal intervention (if not, patients can be randomised to have their allocated infra-popliteal intervention at the same time or after the inflow procedure).	Are a non-English speaker where translation services are inadequate to provide informed consent
Be judged suitable for both vein bypass and best endovascular treatment following diagnostic imaging and a formal documented multi-disciplinary team meeting.	Are judged unsuitable for either revascularisation strategy by the responsible clinician
	Tissue loss considered to be primarily of venous aetiology

	Completed Form	Screen	Baseline	Randomization	Intevention (initial within 2 weeks)	Follow-up months 1, 3, 6, 9, 12, 18, 24,36
Informed Consent	Patient	☑	☑			
History	Case Notes/Patient	☑	☑			
Physical	Case Notes		☑			
Imaging	Case Notes		☑			
Wound Assessment	Case Notes		☑			☑
Ischaemic Pain VAS	Patient		☑			☑
WiFI	Case Notes		☑			☑
HADS	Patient		☑			☑
EQ-5D-5L	Patient		☑			☑
SF-12	Patient		☑			☑
ICECAP-O	Patient		☑			☑
VascuQoL	Patient		☑			☑
Haemodynamic changes	Case Notes		☑			☑
Ulcer and gangrene assessment	Case Notes		☑			☑
Amputation assessment* If applicable complete Amputation Form	Case Notes/Patient		☑		☑	☑
Randomization	Case Notes			☑		
Vascular re-intervention review* If applicable complete an intervention form	Case Notes/Patient				☑	☑
Resource Usage* If applicable complete an In-Patient Form	Case Notes/Patient					☑
Pain Relief Medication Review	Case Notes/Patient		☑			☑
SAE Review	Case Notes/Patient				☑	☑

Fig. 2 The BASIL-2 assessment schedule

Follow-up

Outcomes will be recorded at 1 month after intervention and at 3, 6, 9, 12, 24, 30, and 36 months after randomisation (Fig. 2). Information collected will include further interventions (vascular or non-vascular), hospitalisations (for whatever reason), other health problems, clinical and haemodynamic status of trial and non-trial limbs, functional status and quality of life assessments. The recording of Adverse Events and Serious Adverse Events will conform to the Good Clinical Practice standards and the Research Governance Framework 2005 [8, 9]. After delivery of the randomised intervention, all subsequent interventions will be at the discretion of the clinical team in the patient's best interests.

Sample size calculation

Sample size allocation was calculated on a time-to-event analysis, undertaken at 2 years post randomisation. Recruitment is aiming to take place over 3 years with 20 % recruited in the first year and 40 % recruited in each subsequent year. Non-event rates for amputation-free survival are assumed to be 0.72, 0.62, 0.53, 0.47 and 0.35 at years 1 to 5 based on data from the original BASIL-1 trial [4]. Allowing for a conservative estimate of 10 % drop-out rate for the primary outcome, a trial of 600 patients will have 90 % power to detect a reduction in amputation-free survival of one third (HR = 0.66 equivalent to an absolute difference of 12 % in amputation free survival at Year 3) with a 5 % significance level.

Pilot phase

Recruitment will be reviewed at the end of a 12 month pilot phase. The following are proposed as criteria on which to base a decision to discontinue the trial at that stage:

- Less than 2/3 of the centres recruiting.
- Fewer than 60 patients randomised in total.
- Less than 2/3 of centres recruiting fewer than two patients per month after month 4 onward.

- Less than 80 % of patients have received their allocated treatment.

At the end of the pilot phase, the completeness of the quality-of-life data will also be assessed. If completion rates are poor, then consideration will be given to discontinuing the Hospital Anxiety and Depression Scale and ICEpop CAPability for older people tools.

Repeat and cross-over interventions

Repeat and cross-over interventions are permitted in either arm of the trial if the primary intervention is unsuccessful. After reviewing the data from the original BASIL trial [4], we estimate a 20 % re-intervention rate, which we believe is more likely to occur in the best endovascular treatment arm and within the first 12 months of the primary intervention. Data will be collected on all re-interventions. Re-intervention rates will be compared in a secondary analysis (the trial is powered at 90 % to detect a two-fold difference of 10 % versus 20 %).

Subgroup analysis

Subgroup analysis will be used to detect treatment effects between pre-specified variables, focusing on effects on survival and repeated measures models (Table 3).

Economic evaluation

An economic evaluation will be undertaken to determine the relative cost-effectiveness of the 'vein bypass first' and 'best endovascular first' revascularisation strategies with a view to informing clinical decision-making within the NHS. The economic analysis will consist of two components: a 'within-study' analysis which will be based on study end-points and a 'model-based' analysis which will extrapolate and compare costs and effects likely to accrue beyond the study follow-up period. The analysis will be presented in terms of cost per additional quality-adjusted life year gained and cost per year of amputation-free survival. In line with existing recommendations, the base-case analysis will adopt a health care system (payer's) perspective by considering costs incurred by the NHS and personal social services. Costs will be calculated on the basis of patient-level data related to (a) the procedures under assessment; (b) hospital stay and re-admissions, and (c) post-discharge use of National Health Service and social services. Procedure-related costs will be estimated in a separate micro-costing study. If plausible, additional analyses will be undertaken from a wider societal perspective. Quality of life will be derived from patients' responses to the EuroQol EQ-5D-5 L [10] instrument and will be translated into preference-based quality of life indices using a UK-specific valuation set [11]. In addition to the trial-based evaluation, a model-based analysis will be conducted to consider the costs and benefits likely to accrue over a lifetime time horizon. Both deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and plausible variations in key assumptions and employed analytic methods [12].

Table 3 BASIL-2 sub-group analysis

Rest pain versus tissue loss versus both
Diabetes mellitus
CKD
Haemodynamic measurements
Alternative endovascular options
Differences in resource usage and outcome between alternative endovascular options

Interim analyses

Interim analyses will be performed on an annual basis. A Haybittle-Peto approach will be used where all interim analyses use a difference of three standard errors as a stopping guideline. These analyses will be reviewed by the independent data monitoring committee on an annual basis or more frequently if required.

Differences in the primary clinical outcome (amputation-free survival) will be assessed by comparing time from randomisation to major (above ankle) limb amputation or death from any cause (whichever occurs first) between the two arms. Primary analysis will use Kaplan-Meier plots and test the difference between two arms using the log-rank test. Data will be censored when individuals reach the end of follow-up or are lost to follow-up before incurring the primary outcome.

Further analysis of the primary outcome will involve the fitting of flexible parametric survival models to estimate both relative and absolute differences in hazard of the primary outcome to model the underlying differences in hazard and to allow for non-proportional hazards. The addition of covariates to the model, derived from the minimisation variables (age, sex, presence or absence of chronic kidney disease, diabetes and tissue loss) will allow baseline adjustments and the ability to test for further subgroup effects. The primary analysis will be performed on an intention to treat basis taking into consideration the first allocated method of revascularisation, regardless of cross-over or repeat interventions.

Secondary outcome measures that are based on continuous scales will be examined using a repeated measures multi-level model to examine the effects over time. Treatment effects will be reported from these measures at 1 and 12 months from randomisation and at the end of the study. Other outcomes will be measured using standard statistical methods, such

as Fisher's exact test for categorical data and log-rank for time to event data. All of these analyses will be performed using the intention to treat principle with 95 % confidence intervals with associated *p*-values.

Discussion

The trial is designed to be pragmatic and representative of the 'real world' NHS management of severe limb ischaemia due to infra-popliteal disease. Many of these patients will have multi-level disease including 'inflow' or aorto-iliac disease, which may need to be corrected prior to randomisation. With the evolution of hybrid operating it would be permissible to perform an on-table inflow procedure (to popliteal, knee, level) at the same time as the randomised infra-popliteal intervention. Alternatively, an inflow procedure to popliteal (knee) level can be performed first and the patient then randomised if further infra-popliteal intervention is considered necessary.

Data from the original BASIL-1 trial [4] suggests that up to 25 % of patients may present with bilateral severe limb ischaemia. Bilateral simultaneous revascularisation is rare. It is usually clinically obvious which leg requires revascularisation first. Only one leg can be randomised in BASIL-2.

Patients can only be randomised if clinical equipoise exists. Local variations in practice may influence such decisions with some centres likely to favour an endovascular intervention strategy and others preferring surgical bypass. Current evidence does not support either an endovascular first or bypass first strategy and unless an obvious clinical reason is evident (such as lack of vein conduit, unsuitability for a surgical intervention due to comorbid state) all patients who are suitable for both arms could, theoretically be randomised into the trial.

Trial status

The BASIL-2 trial is currently open for recruitment in multiple UK-based centres and has randomised more than 100 patients at the time of publication.

Abbreviations

BASIL: Bypass versus Angioplasty in Severe Ischaemia of the Leg; CG: clinical guideline; EQ-5D-5 L: European Quality of Life-5 dimensions-5 levels; HR: Hazard Ratio; ICECAP-O: ICEpop CAPability measure for Older people; ISRCTN: International Standard Randomised Control Trial Number; NHS: National Health Service; PEDIS: Perfusion, Extent, Depth, Infection, Sensation foot score; SF-12: Short Form 12 QoL questionnaire; UK: United Kingdom; VascuQoL: Vascular QoL Questionnaire; WIFI: Wound Ischaemia Foot Infection score.

Competing interests

The authors have no competing interests to declare.

Authors' contribution

All authors have read and approved the final version of this manuscript. MP is responsible for the preparation and drafting of the manuscript. HD is responsible for assistance with manuscript writing and proof reading. HJ is the trial manager and assisted in preparation of the manuscript. GB is the lead research nurse for the trial and assisted in proof reading the manuscript. MG is the operations manager of the clinical trials unit and assisted in proof reading the manuscript for accuracy. SP provided statistical assistance including critical review of the statistics section. SM provided statistical assistance including critical review of the statistics section. LA is a health economist working on the trial and provided advice regarding the writing of the Health Economics section. TR is the lead health economist for the trial and provided advice regarding the writing of the Health Economics section. JD is the director of the clinical trials unit and is responsible for critical review of the manuscript. AB is the chief investigator and primary grant holder and is responsible for trial conception, design and final approval of this manuscript.

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Acknowledgements

This project was funded by the National Institute for Health Research (project number 12/35/45).

Department of Health disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

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Received: 28 May 2015 Accepted: 9 December 2015
Published online: 06 January 2016

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APPENDIX 2: BASIL-2 Screening Consent Form

BASIL-2 Screening Form

COMPLETE FOR ALL PATIENTS ENTERING THE VASCULAR SERVICE WITH A DIAGNOSIS OF SEVERE LIMB ISCHAEMIA AND WHO HAVE CONSENTED TO ENTER SCREENING

Patient Details

Hospital Name: _____

Date of Birth: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy) Patient Initials: ☐☐☐

Date Screened:__ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy) Version of screening consent form: __.__

Hospital Number: ☐☐☐☐☐☐☐☐ NHS Number: ☐☐☐☐☐☐☐☐☐☐

Reasons for Non-Randomisation

Is the patient suitable for entry into BASIL-2?

☐ **YES** – please obtain **Informed Consent** and, if given, continue to **Randomisation Form**

☐ **NO** - please answer **ALL** questions below

	No	Yes
Anatomically unsuitable?		
Has Infra-Popliteal (IP) ± Femoro-Popliteal (FP) disease	☐	☐
Clinically unsuitable?		
No useable vein	☐	☐
MDT thinks patient should have Vein Bypass (VB)	☐	☐
MDT thinks patient should have Best Endovascular Treatment (BET)	☐	☐
MDT thinks patient should have primary amputation	☐	☐
MDT thinks patient should be treated conservatively (i.e. without VB, BET or amputation)	☐	☐
MDT thinks patient should have prosthetic bypass	☐	☐
Other possible exclusions?		
Patient lacks capacity to provide written informed consent	☐	☐
Patient lacks adequate English and translation services are insufficient at the relevant hospitals to ensure informed consent	☐	☐
Patients life expectancy is thought to be <6 months	☐	☐
Patient declined to enter study (please give reason if they are willing to tell you)	☐	☐

Reason _____

☐ Other (please specify) :

_____

Completed by (name): _____

Signed:_____ Date: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy)

CONFIDENTIAL WHEN COMPLETED

APPENDIX 3: BASIL-PCS Baseline Data Collection Form

SLI Registry Pilot Proforma

Patient Details

Audit Number: ☐☐☐☐ Please confirm which leg: Right ☐ Left ☐

Patient Initials: ☐☐☐ Unit Number_____

Date of Birth: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy)

Height: ☐☐☐.☐ cm | Weight: ☐☐☐.☐ kg

Risk Factors for SLI

Chronic Kidney Disease (CKD): CKD defined as stage 3 or worse based on estimated GFR of < 60 (ml/min/1.73m^2)	☐ No	☐ Yes			
Stroke:	☐ No	☐ Yes	MI: ☐ No	☐ Yes	Angina: ☐ No ☐ Yes
CABG:	☐ No	☐ Yes	PCI: ☐ No	☐ Yes	Dialysis: ☐ No ☐ Yes

Diabetes: ☐ No ☐ Yes **If "Yes"**, indicate type ☐ Type 1 ☐ Type 2

If "Yes" to diabetes, are they Insulin Dependent: ☐ No ☐ Yes

Previous Vascular Intervention (tick all that apply)

Left Leg	☐ No	☐ Yes	**Right Leg:**	☐ No	☐ Yes
Endovascular:	☐ No	☐ Yes		☐ No	☐ Yes
Surgery:	☐ No	☐ Yes		☐ No	☐ Yes
Minor Amputation:	☐ No	☐ Yes		☐ No	☐ Yes
Below Knee Amputation:	☐ No	☐ Yes		☐ No	☐ Yes
Above Knee Amputation:	☐ No	☐ Yes		☐ No	☐ Yes

Mobility

☐ Fully ambulant without walking aid ☐ Ambulant with walking aid ☐ Wheelchair bound ☐ Bed-bound

Smoking Status

☐ Never ☐ Ex ☐ Current If "ex" or "current" please give number of pack years ☐☐☐

Ethnicity *(tick one only)*	**White**	**Black / Black British**
	☐ British	☐ Caribbean
	☐ Irish	☐ African
	☐ Other White _____	☐ Other Black _____
Asian / Asian British	**Mixed**	**Chinese or Other Ethnic Group**
☐ Indian	☐ Mixed White/ Black Caribbean	☐ Chinese
☐ Pakistani	☐ Mixed White/ Black African	☐ Any Other _____
☐ Bangladeshi	☐ Mixed White/ Asian	☐ Not given
☐ Other Asian_____	☐ Other Mixed Background _____	

BASIL-2 Baseline Clinical Assessment Form

Haemodynamic Status

Right Brachial Systolic BP: __ __ __ mmHg			Left Brachial Systolic BP: __ __ __ mmHg		
Right Leg: NF = not found, NC = not compressible			**Left leg**: NF = not found, NC = not compressible		
DP: __ __ __ mmHg	☐ NF	☐ NC	DP: __ __ __ mmHg	☐ NF	☐ NC
PT: __ __ __ mmHg	☐ NF	☐ NC	PT: __ __ __ mmHg	☐ NF	☐ NC
PP: __ __ __ mmHg	☐ NF	☐ NC	PP: __ __ __ mmHg	☐ NF	☐ NC
Hallux: __ __ __ mmHg	☐ NF		Hallux: __ __ __ mmHg	☐ NF	

	Right Leg	Left Leg
Ischemic Rest Pain:	☐ No ☐ Yes	☐ No ☐ Yes
Tissue Loss*: (If present, tick all that apply)	Present ☐ No ☐ Yes	Present ☐ No ☐ Yes
	Hallux ☐ No ☐ Yes	Hallux ☐ No ☐ Yes
	Other Toes ☐ No ☐ Yes If yes, number of toes ☐	Other Toes ☐ No ☐ Yes If yes, number of toes ☐
	Forefoot ☐ No ☐ Yes	Forefoot ☐ No ☐ Yes
	Hind Foot ☐ No ☐ Yes	Hind Foot ☐ No ☐ Yes
	Ankle ☐ No ☐ Yes	Ankle ☐ No ☐ Yes
	Above Ankle ☐ No ☐ Yes	Above Ankle ☐ No ☐ Yes

Medical Therapy

Aspirin? ☐ No ☐ Yes	Clopidogrel? ☐ No ☐ Yes	Other Anti-platelet ☐ No ☐ Yes*			
*If Yes, please specify _____					
On treatment for Hypercholesterolemia: ☐ No ☐ Yes		On treatment for Hypertension: ☐ No ☐ Yes			
Warfarin: ☐ No ☐ Yes	Other Anticoagulant: ☐ No ☐ Yes (please specify) _____				
Paracetamol	☐ No ☐ Yes	Opiates	☐ No ☐ Yes	NSAIDs	☐ No ☐ Yes
Gabapentin	☐ No ☐ Yes	Amitriptyline	☐ No ☐ Yes		

Imaging witihin the last 12 months

Imaging Method:	☐ Duplex US	☐ MRA	☐ CTA	☐ DSA

PEDIS

Perfusion Status

- ☐ Grade 1: no symptoms/signs of Peripheral Artery Disease (PAD)
- ☐ Grade 2: symptoms or signs of PAD, but not Sever Limb Ischaemia (SLI)
- ☐ Grade 3: CLI

Extent of tissue loss ☐☐ ☐☐ cm^2

Infection

- ☐ Grade 1: no symptoms/signs
- ☐ Grade 2: Inflammation of skin/subcutaneous only
- ☐ Grade 3: Extensive erythema deeper than skin/subcutaneous
- ☐ Grade 4: Systemic inflammatory response syndrome (SIRS)

Depth of tissue loss

- ☐ Grade 1: Superficial full-thickness ulcer
- ☐ Grade 2: Ulcer penetrating below dermis to skin structures
- ☐ Grade 3: All subsequent layers of foot, including bone/joint

Sensation

- ☐ Grade 1: No loss of protective sensation
- ☐ Grade 2: Loss of protective sensation

Baseline Assessment WIFI + Outcomes

Wound Status

Indicate Grade below	Grade	Clinical Description
☐	0	Ischemic rest pain; Pre-gangrenous skin change, without frank ulcer or gangrene (Pedis or UT Class 0)
☐	1	Minor tissue loss: small shallow ulceration) < 5 cm2 on foot or distal leg (Pedis or UT Class 1); no exposed bone unless limited to distal phalanx (maximum digital amp x 1-2)
☐	2	Major tissue loss: deeper ulceration(s) with exposed bone, joint or tendon, ulcer 5-10 cm2 not involving calcaneus –(Pedis or UT Classes 2 and 3); gangrenous changes limited to digits. Salvageable with multiple (> 3) digital amps or standard TMA + skin coverage
☐	3	Extensive ulcer/gangrene > 10 cm2 involving forefoot or midfoot; full thickness heel ulcer > 5 cm2 + calcaneal involvement. Salvageable only with complex foot reconstruction, nontraditional TMA (Chopart/Lisfranc); flap

Ischaemic Status

Indicate Grade below	Grade	ABPI	Ankle SP (mm Hg)	TP $TcpO_2$ (mm Hg)
☐	0	>0.80	>100	>60
☐	1	0.60-0.79	70-99	40-59
☐	2	0.40-0.59	50-69	30-39
☐	3	< 0.40	< 50	< 30

Foot Infection

Indicate Grade below	Grade	Clinical Description
☐	0	Wound without purulence or manifestations of infection
☐	1	>2 manifestations of infection (erythema or purulence, pain, tenderness, warmth or induration) any cellulitis or erythema extends, 2cm around ulcer; infection is limited to skin or subcutaneous tissues; no local complications or systemic illness
☐	2	Infection in patient who is systemically and metabolically stable but has ≥1 of the following: cellulitis extending 2cm, lymphangitis; spread beneath fascia;
☐	3	Infection in patient with systemic or metabolic toxicity

Summary of Admission

Date of Admission: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy)

Date of Discharge: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy)

Days in Hospital: ☐☐☐ Ward ☐☐☐ HDU ☐☐☐ ITU

Died in Hospital: ☐ No ☐ Yes **If "Yes"**, Date Died: __ __ / __ __ __/ __ __ __ __ (dd/mmm/yyyy)

If the patient has died, please complete a BASIL-2 Exit Form

Discharged to: ☐ Own Home ☐ Other Acute Hospital ☐ Residential Home ☐ Nursing Home

Other (please specify) _____

Did the patient have **vascular intervention**? ☐ No ☐ Yes (tick all that apply)

If yes, was it ☐ Surgical ☐ Endovascular ☐ Minor Amputation ☐ Major Amputation

APPENDIX 4: Publications Arising from This Thesis

Eur J Vasc Endovasc Surg (2017) ■, 1–7

A Comparison of Outcomes in Patients with Infrapopliteal Disease Randomised to Vein Bypass or Plain Balloon Angioplasty in the Bypass vs. Angioplasty in Severe Ischaemia of the Leg (BASIL) Trial

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WHAT THIS PAPER ADDS

These data reconfirm the need for further publicly funded, unbiased, pragmatic randomised controlled trials, such as BASIL-2 and BEST-CLI, to compare the clinical and cost effectiveness of infra-popliteal vein bypass and best endovascular treatment in patients suitable for both interventions.

Objective: The aim was to compare outcomes in a subgroup of patients with infrapopliteal (IP) disease randomised to infrapopliteal vein bypass (VB) or plain balloon angioplasty (PBA) in the original BASIL trial.

Methods: A comparison of outcomes from patients randomised to VB or PBA undergoing revascularisation for severe limb ischaemia (SLI) because of IP disease with or without femoropopliteal disease. Data were extracted from case report forms from the BASIL trial. The primary outcome was amputation free survival (AFS); secondary outcomes included overall survival (OS), 30 day mortality and morbidity, freedom from arterial re-intervention, immediate technical success, repeat and crossover interventions, length of hospital stay, and quality of revascularisation.

Results: A total of 104 patients were identified in the BASIL study with IP disease, 56 randomised to IP VB, and 48 to IP PBA. Groups were similar at baseline except for more chronic kidney disease and non-steroidal anti-inflammatory drug use in the VB group, and more previous surgical arterial intervention and antihypertensive use in the PBA group. There were no statistically significant differences in AFS or OS; however, clinically important trends were apparent in favour of a VB first strategy. Patients allocated to VB demonstrated significantly quicker relief of rest pain when compared with PBA ($p = .005$), but no significant differences in improved tissue healing. Median length of index hospital admission was significantly greater in the VB than in the PBA group (18 vs. 10 days, $p < .0001$) but there was no difference between the two groups in median total hospital stay between randomisation and the primary endpoint (VB 43.5 vs. PBA 42 days).

Conclusions: Further randomised trials, like BASIL-2 and BEST-CLI, are required to determine whether patients with severe limb ischaemia who require IP revascularisation and who are suitable for VB should have bypass or endovascular intervention as their primary revascularisation procedure.

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Article history: Received 18 October 2016, Accepted 20 April 2017, Available online XXX

Keywords: BASIL trial, Critical limb ischaemia, Infrapopliteal, Vein bypass, Plain balloon angioplasty

INTRODUCTION

The UK National Institute of Heath Research (NIHR) Health Technology Assessment (HTA) funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial remains the only published randomised controlled trial (RCT) to compare bypass surgery with angioplasty for the treatment of severe limb ischaemia (SLI) comprising rest pain, tissue loss, or both (http://www.nets.nihr.ac.uk/projects/hta/960501).[1]

The BASIL trial randomised 452 patients with SLI, defined as rest pain, tissue loss, or both because of atherosclerotic peripheral arterial disease, to bypass surgery (75% with vein) or plain balloon angioplasty (PBA) (6 patients also had bare metal stents). Around 25% of patients underwent revascularisation for SLI as a result of infrapopliteal (IP) disease with or without femoropopliteal (FP) disease; however, the trial was not powered to demonstrate effects in this subgroup. In patients who survived more than 2

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http://dx.doi.org/10.1016/j.ejvs.2017.04.020

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years after randomisation, bypass was associated with a better outcome in terms of amputation free survival (AFS) and overall survival (OS). By contrast, in patients who did not survive for 2 years, there was no significant clinical difference between the two treatment arms in terms of major amputation or mortality.

In August 2012, the UK National Institute for Health and Care Excellence (NICE) published its national Clinical Guidelines (CG 147) on Peripheral Arterial Disease (https://www.nice.org.uk/guidance/cg147).[2] Although the multidisciplinary expert guideline committee mainly based its recommendations on SLI revascularisation strategies on data from the BASIL trial, it recognised that BASIL was primarily a trial of FP interventions. As such, the committee's view was that there remained considerable uncertainty as to whether SLI patients requiring an IP revascularisation, and who could have distal vein bypass (VB), should receive VB or best endovascular therapy (BET) as their first revascularisation procedure. For this reason, NICE recommended a further RCT in this area and NIHR HTA subsequently funded the BASIL-2 trial, which compares the clinical and cost effectiveness of VB and BET for the treatment of SLI due to IP disease (http://www.nets.nihr.ac.uk/projects/hta/123545).[3]

Although there seems to be broad agreement that this is an important question, recruitment to BASIL-2 has been difficult. This is mainly because, despite a lack of supporting evidence, a significant body of vascular surgeons and interventional radiologists believe that a BET first revascularisation strategy is clearly preferable for most, even all, patients with SLI due to IP disease, and that VB should be reserved for those who cannot have or fail BET.

To generate discussion around the question posed by BASIL-2, clinical outcomes have been compared in a subset of patients randomised to IP VB or PBA within the original BASIL trial.

METHODS

During the trial, 452 patients with SLI as a result of infrainguinal disease were randomised between August 1999 and June 2004 from 27 different UK hospitals to a VB first or PBA first strategy. The original BASIL case report forms (CRFs) were interrogated for those patients randomised to IP VB or PBA. Patients in this subgroup had either PBA with or without bare metal stent or VB with the distal target vessel below the popliteal artery (including the tibioperoneal trunk and beyond). Patients with grafts using prosthetic material were excluded (including composite sequential), as this no longer reflects current clinical practice (Fig. 1).

The primary outcome was AFS; secondary outcomes included OS, 30 day mortality and morbidity, freedom from arterial re-intervention, immediate technical success rates, repeat and crossover interventions, and length of hospital stay. The quality of revascularisation was also assessed in terms of improvement in ankle brachial pressure index (ABPI), number of days to cessation of rest pain, and healing of ischaemic wounds and/or 'minor' amputations.

Time to event outcomes were recorded over 5 years of follow-up and are presented using Kaplan–Meier plots. Differences between groups are estimated as hazard ratios (HR) computed from the log-rank statistic. The authors present 95% confidence intervals for each HR to describe

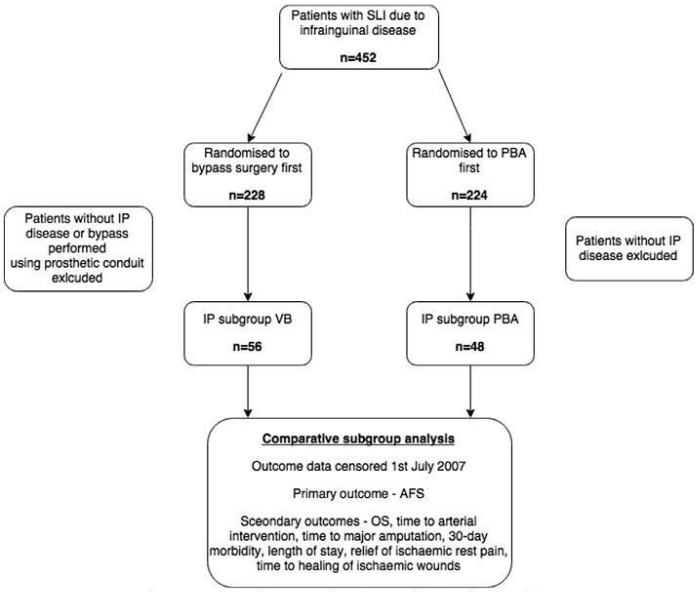


Figure 1. Flow diagram of patient selection for analysis.

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the range of treatment effects compatible with the observed data. Differences in other outcomes are assessed using *t* tests, chi-square tests and Wilcoxon rank sum tests according to data type and distributional shape. All analyses were performed an intention-to-treat analysis with data censored on 1 July 2007. Analyses were undertaken in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The 56 patients randomised to IP VB and the 48 to IP PBA were generally similar at baseline except in the VB group twice as many patients had chronic kidney disease (34% VB vs. 15% PBA) and twice as many were current smokers (25% vs. 11%); they also a had higher use of non-steroidal anti-inflammatory drugs (23% vs. 6%). In the PBA group twice as many patients had a history of previous myocardial infarction (14% VB vs. 29% PBA) and more patients had a history of hypertension on current antihypertensive treatment (61% VB vs. 79% PBA). Previous vascular intervention was more common in the PBA group. In this group, five patients had undergone previous suprainguinal PBA, three patients had previous infrainguinal PBA, one patient had previous infrainguinal surgery, one patient had both previous infrainguinal surgery and infrainguinal PBA, two patients had previous suprainguinal surgery, and one patient had undergone previous minor amputation surgery. Conversely in the VB group two patients had undergone previous suprainguinal PBA, one patient had previous infrainguinal PBA, one patient had previous infrainguinal surgery, one patient had previous suprainguinal PBA with stenting and concurrent infrainguinal PBA, and one patient had previous PBA in an unrecorded anatomical segment. Baseline comparisons are presented in Table 1. Procedural details, describing anatomical variation and target vessel lesions are reported in Tables 2 and 3. Only single vessel recanalisation was attempted in the majority of patients undergoing PBA (85%), with 15% of patients undergoing two vessel recanalisation attempts and no patients undergoing three tibial vessel recanalisation.

Primary technical success (during the BASIL trial technical success was documented by the responsible surgeon or interventionalist at the time of procedure, the criteria for this was left to the discretion of the investigator) was higher for VB (86%) than for PBA (73%) (RR for technical failure 0.53, 95% CI 0.24−1.16, $p = .11$). In four patients randomised to VB, surgery was discontinued due to a lack of an appropriate IP target vessel; another four patients suffered graft failure within 24 h. Three patients had attempted graft thrombo-embolectomy; one graft was salvaged as a result of this, whereas two patients underwent delayed major lower limb amputation. In the PBA group, it proved

Table 1. Baseline characteristics.

	Vein bypass ($n = 56$)	Plain balloon angioplasty ($n = 48$)	*p*
Age, years (mean, SD)	74.0 (11.3)	77.2 (7.3)	.09
Male sex	41 (73%)	32 (67%)	.5
Comorbidities			
Chronic kidney disease	19 (34%)	7 (15%)	**.007**
Stroke/TIA	12 (21%)	8 (17%)	.5
Myocardial Infarction	8 (14%)	14 (29%)	.06
Angina	11 (20%)	10 (21%)	.9
Dialysis	2 (4%)	0 (−)	.2
Diabetes (DM)	24 (43%)	23 (48%)	.6
Insulin dependent DM	10 (42%)	8 (35%)	.6
Smoking status			
Current	14 (25%)	5 (11%)	.1
Ex	29 (52%)	27 (56%)	
Never	13 (23%)	16 (33%)	
Clinical presentation			
Tissue loss	46 (82%)	41 (85%)	.7
Medical therapy			
Aspirin	38 (68%)	25 (52%)	.1
Clopidogrel	4 (7%)	3 (6%)	.9
Antihypertensive	34 (61%)	38 (79%)	**.04**
Statin therapy	22 (39%)	12 (25%)	.1
Warfarin	4 (7%)	5 (10%)	.6
Paracetamol	36 (64%)	29 (60%)	.7
Opiates	31 (55%)	28 (58%)	.8
NSAIDs	13 (23%)	3 (6%)	**.02**
Gabapentin	2 (4%)	1 (2%)	.7
Amitriptyline	5 (9%)	2 (4%)	.3
Previous intervention			
Endovascular	5 (9%)	7 (15%)	.4
Surgical	1 (2%)	6 (13%)	**.03**

p value in bold demonstrates statistical significance (95% confidence)

Table 2. Vein bypass procedure details.

$n = 56$		Number
Conduit	Reversed vein	24 (43%)
	Non-reversed vein	28 (50%)
	Leg vein	51 (91%)
	Arm vein	1 (2%)
	No bypass performed as distal target not patent	4 (7%)
Proximal anastomosis	Common femoral artery	24 (43%)
	Superficial femoral artery	18 (32%)
	Profunda femoris artery	1 (2%)
	Above knee popliteal artery	5 (9%)
	Below knee popliteal artery	5 (9%)
Distal anastomosis	Posterior tibial artery 1/3	3 (5%)
	Posterior tibial artery 2/3	4 (7%)
	Posterior tibial artery 3/3	10 (18%)
	Tibio-peroneal trunk	1 (2%)
	Peroneal artery 1/3	5 (9%)
	Peroneal artery 2/3	5 (9%)
	Peroneal artery 3/3	4 (7%)
	Anterior tibial artery 1/3	6 (11%)
	Anterior tibial artery 2/3	5 (9%)
	Anterior tibial artery 3/3	6 (11%)
	Dorsalis pedis	2 (4%)
Technical failures	Graft completed but failed < 24 h	4 (7%)
	Abandoned, no outflow vessel	4 (7%)
	Total technical failure	8/56 (14%)

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Table 3. Plain balloon angioplasty procedure details.

$n = 48$		Number
Arteries treated	Superficial femoral	29 (60%)
	Above knee popliteal	29 (60%)
	Below knee popliteal	28 (58%)
	Tibio-peroneal Trunk	4 (8%)
	Posterior tibial	9 (19%)
	Peroneal	25 (52%)
	Anterior tibial	19 (40%)
	Dorsalis pedis	1 (2%)
Attempted number of tibial vessel recanalisations	1 vessel	41 (85%)
	2 vessels	7 (15%)
	3 vessels	0 (-%)
Type of disease treated	Occlusive	23 (48%)
	Stenotic	12 (25%)
	Combination	13 (27%)
PBA and stent use	PBA only	47 (98%)
	PBA + Bail out BMS	1 (2%)
Technical failure	Inability to cross lesion	6 (12%)
	Recoil (failed angioplasty)	5 (10%)
	Embolism	1 (2%)
	Abandoned at patient request	1 (2%)
	Total technical failure	13/48 (27%)

impossible to cross and/or dilate the IP lesion in 10 (21%) patients; in two patients, there was distal embolisation/vessel rupture that halted the procedure; and one procedure was abandoned due to pain. From these 13 patients, four went on to have VB, four had no further intervention, three had a repeat attempt at PBA, one had a below knee amputation (BKA), and one patient underwent common femoral endarterectomy and profundaplasty.

AFS was 32% lower in the PBA group than VB group (HR 0.68, 95% CI 0.42—1.10, $p = .1$) (Fig. 2) and OS 40% lower in the PBA group (HR = 0.60, 95% CI 0.36—1.02, $p = .06$) (Fig. 3). Removing patients with prior arterial intervention from the analysis did not have any effect on outcome in terms of AFS ($p = .5$) or OS ($p = .3$). Similarly, when viewed

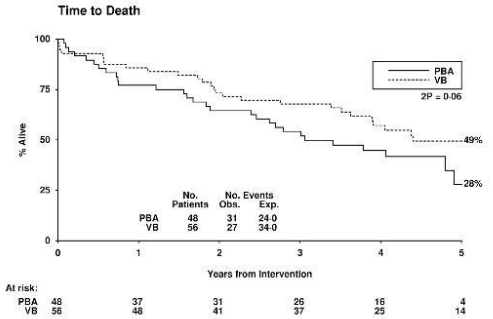


Figure 3. Overall survival. HR 0.60, 95% CI 0.36—1.02, $p = .06$.

as a whole, cohort patients with IP disease with prior intervention did not demonstrate significantly poorer AFS than patients with de novo lesions ($p = .3$). Time to arterial re-intervention (Fig. 4) or time to major amputation (Fig. 5) were similar in both arms, but clinically important halving or doublings of events could not be ruled out for either treatment. Mortality 30 days after the index procedure was not significantly different (4 patients, 7% VB group vs. 1 patient, 2%, in the PBA group, $p = .2$). The most common causes of death were pneumonia and heart related disease (12 patients and 20 patients respectively) (Table 4). Patients in the VB group were more likely to suffer morbidity within 30 days with more wound infections, sepsis and cardiovascular complications than patients in the PBA group (RR 2.86, 95% CI 1.25—6.53, $p = .01$) (Table 5).

In the VB group, nine patients had below knee amputation (BKA) and four had an above knee amputation (AKA) compared with six BKA and four AKA in the PBA group. Only one patient, who was in the VB group, had revision of a BKA to a higher level. Distribution of tissue loss was similar between the groups with most patients having gangrene or ulceration restricted to the digits (74% VB, 71% PBA).

The median length of index hospital admission was significantly greater in the VB group (18 vs. 10 days, $p < .0001$) but there was no difference in total median

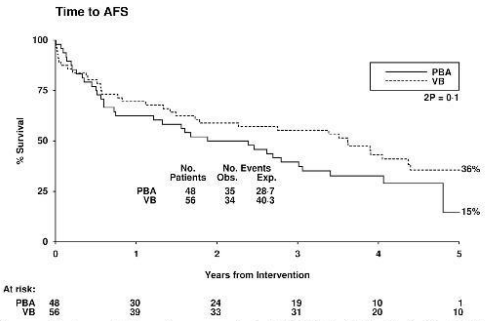


Figure 2. Amputation free survival. HR 0.68, 95% CI 0.42—1.10, $p = .1$.

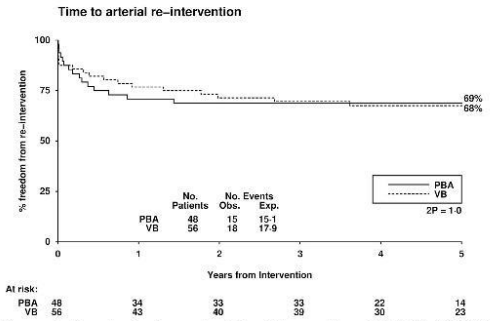


Figure 4. Time to further arterial re-intervention. HR 1.01, 95% CI 0.51—2.00, $p = 1.0$.

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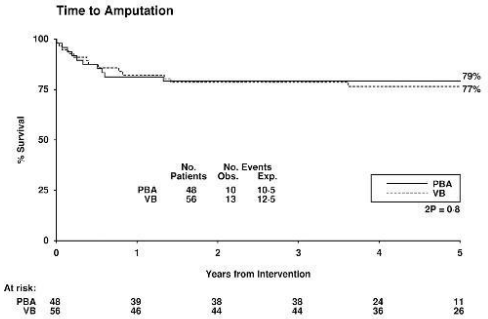


Figure 5. Time to major amputation. HR 1.10, 95% CI 0.48—2.49, $p = .8$.

hospital stay between randomisation and the primary endpoint (43.5 days VB vs. 42 days PBA).

In the PBA and VB groups, 85% and 77% patients had pre- and post-procedure ABPI measurements. The mean pre-intervention ABPI in the VB group was 0.53 (SD 0.38), which improved to 0.93 (SD 0.42) post intervention. In the PBA group mean pre-intervention ABPI was 0.43 (SD 0.27), which improved to 0.85 (SD 0.32). The mean improvement in ABPI was 0.42 (SD 0.36) and 0.37 (SD 0.38), respectively ($p = .18$).

In terms of the quality of revascularisation, time to healing of tissue loss was 70% higher in favour of VB than PBA, although this was not statistically significant (HR 1.69, 95% CI 0.88—3.26, $p = .1$) (Fig. 6). Relief of ischaemic rest pain was more than twice as common in the VB group (HR 2.19, 95% CI 1.27—2.78, $p = .005$) with more patients pain free at 5 years (Fig. 7).

Eight (17%) people in the PBA group went on have bypass compared with eight people (14%) in the VB group who went on to have PBA. Patients who underwent primary angioplasty that failed and went on to VB had no differences in AFS compared with patients undergoing primary VB. Likewise, no difference in AFS was seen in patients who underwent primary VB and went on to have secondary PBA.

DISCUSSION

Despite being underpowered, this analysis of the subgroup of IP patients receiving revascularisation for SLI provides some thought provoking evidence. Although the clinical

Table 5. Thirty day morbidity.

Cause	VB	PBA	p
Bleeding	2 (4%)	1 (2%)	.7
Sepsis (urine, chest, CD colitis)	4 (7%)	2 (4%)	.5
Wound infection	8 (14%)	2 (4%)	.08
Myocardial infarction	3 (5%) (all fatal)	0 (—)	.1
Cerebrovascular accident	1 (2%)	0 (—)	.4
Death from other causes	2 (4%)	1 (2%)	.7
Total	20/56 (36%)	6/48 (13%)	.01

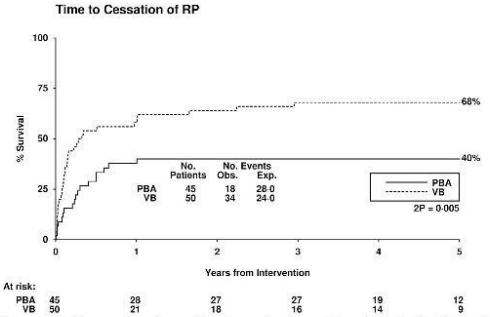


Figure 6. Time to healing of ischaemic tissue loss. HR 1.69, 95% CI 0.88—3.26, $p = .1$.

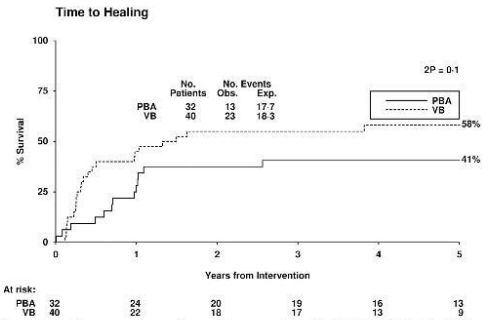


Figure 7. Time to cessation of rest pain. HR 2.19, 95% CI 1.27—3.78, $p = .005$.

Table 4. Cause of death.

Cause	VB	PBA	Total	p
Pneumonia	5	7	12	.4
Other Sepsis	2	3	5	.5
Malignancy	0	3	3	.06
"Old age"	1	1	2	.9
Heart related disease	11	9	20	.9
Other vascular related disease (cerebrovascular accident/peripheral vascular disease/ruptured aortic aneurysm	3	1	4	.4
Not Known	5	7	12	.4
Total	27/56 (48%)	31/48 (65%)	58/104 (56%)	.09

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endpoint analysis did not reach statistical significance there appears to be a positive, clinically important limb salvage and survival advantage in favour of VB in this patient group despite a higher rate of smoking and previous myocardial infarction. Clinical effects in terms of healing of ischaemic wounds were difficult to compare because of lack of detailed information regarding wound severity, depth, extent, or presence of infection. Owing to the data available, it was not possible to apply a validated, robust wound scoring system to describe differences, if any, in terms of extent of tissue loss between intervention groups. From the information available (anatomical location of tissue loss and time to complete healing) there was a trend towards improved healing rates in the VB group, although this was not statistically significant. Time to cessation of rest pain from primary intervention was significantly less in the VB group.

We accept that such results should be interpreted with caution given the BASIL trial was not powered to demonstrate treatment effects in the IP subgroup. Results from this study are however thought provoking and demonstrate the need for further higher quality evidence in this patient subgroup. It is also pertinent to note that despite higher 30 day morbidity in the VB group this did not correlate with poorer limb salvage or mortality. Increase in morbidity did, however, lead to a longer inpatient stay during the index admission.

In both groups the median length of hospital stay on index admission was high, the authors believe that the BASIL trial accurately recorded the standard of care for SLI patients in the UK at that point in time. They believe that this was largely because most patients with SLI were emergency rather than elective admissions and a high proportion had tissue loss (approximately 70% in both groups), which often leads to complex social and wound management issues.

Interestingly, there was little or no difference in the length of time spent in hospital between the two groups from randomisation to primary endpoint, suggesting that the early advantage of a shorter length of stay in patients undergoing PBA is lost over a longer period of time when examining all-cause admissions

In both groups, treatment success was arguably low (VB 86% vs. PBA 73%). The original trial analysis was performed on an intention-to-treat analysis. At the time of randomisation, patients were deemed suitable for either intervention based on adequate radiographic assessment and clinical equipoise between both revascularisation strategies. However, in some patients randomised to VB on exploration of the target vessel, the distal bypass vessel was occluded or not suitable for surgical anastomosis. This would represent a similar situation to a failure or inability to cross a target lesion in the PBA group. The trial was designed to be pragmatic and to reflect variations in practice and assessment throughout the UK as no specific guidelines or evidence were available at the time of the original BASIL trial, even now with recent European guidelines[4] practices in imaging assessment and treatment methods vary widely.

The BASIL trial has been criticised by some regarding generalisability, approximately 30% of screened subjects were randomised into the trial. This trend is seen in current clinical trials in patients with SLI as patients present with heterogeneous patterns of anatomical disease, which can make comparisons and equipoise between treatment strategies a barrier to recruitment and inclusion despite a clear lack of evidence to support a first revascularisation treatment strategy.

SLI remains a significant global problem.[5,6] Up to 50% of patients with SLI will have significant IP disease and this proportion may be increasing due to the rising prevalence of diabetes and chronic kidney disease.[7] Unfortunately, the evidence base underpinning the management of SLI resulting from IP disease remains extremely limited.[8–12] Present data indicate that it is far from clear that patients with SLI who require IP revascularisation and who are suitable for VB should have BET as their primary procedure. The technical and clinical failure rate with IP PBA was high; whether this would be materially lower in current practice leading to improved clinical outcomes is a subject of ongoing research.

In conclusion, current data reconfirm the need for further publicly funded, unbiased, pragmatic RCTs, such as BASIL-2[3] and BEST-CLI,[13] to compare clinical and cost effectiveness of IP VB and BET in patients suitable for both interventions.

Ethical approval was granted as part of the original BASIL trial.

CONFLICT OF INTEREST

None.

FUNDING

The original BASIL trial from which these data originate was funded by the NIHR HTA 96/05/01.

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Original Article

Vascular and Endovascular Surgery
1-6
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DOI: 10.1177/1538574419887594
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Comparison of Outcomes Following Infrapopliteal Plain Balloon Angioplasty in the BASIL Trial (1999-2004) and in a Contemporary Series (2009-2013)

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Abstract

Objectives: To compare outcomes in patients randomized to infrapopliteal (IP) plain balloon angioplasty (PBA) for chronic limb-threatening ischemia within the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL)-1 trial between 1999 and 2004 with outcomes in consecutive patients undergoing IP PBA at an academic vascular unit a decade later (2009-2013, Contemporary series [CS]). **Methods:** Individual patient data were obtained from prospective BASIL-1 (48 patients) and CS databases (73 patients). All had a minimum of 3-years of follow-up. Outcomes studied were amputation-free survival (AFS), overall survival (OS), major (above ankle) limb amputation, arterial reintervention, immediate technical success, and length of hospital stay for the index procedure and during the following 12-month period. Statistical analysis was performed using SAS version 9.4. **Results:** The BASIL and CS cohorts were well matched for gender, age, diabetes, previous stroke, myocardial infarction and arterial intervention, and presence of tissue loss. More patients in BASIL-1 underwent concomitant treatment of the superficial femoral (60% vs 37%, $P = .01$) and above knee popliteal (60% vs 34%, $P = .005$) arteries. Immediate technical success increased from 73% in BASIL-1 to 90% in the CS ($P = .01$). Between the two cohorts, there were no differences in AFS (hazard ratio [HR] = 1.00, 95% confidence interval [CI]: 0.65-1.54, $P = 1.0$), OS (HR = 1.04, 95% CI: 0.66-1.62, $P = .9$), major amputation (HR = 0.86, 95% CI: 0.37-1.97, $P = .7$), or reintervention (HR = 0.61, 95% CI: 0.29-1.27, $P = .2$). Contemporary series patients spent significantly fewer days in hospital following the index procedure ($P = .02$) and also over the following 12 months ($P = .002$). **Conclusions:** Despite improvements in the immediate technical angiographic success of IP PBA between BASIL and the CS, there were no significant improvements in survival outcomes. Results from BASIL-2 and BEST-CLI are required in order to properly define the clinical and cost-effectiveness of endovascular treatment in such patients.

Keywords

angioplasty, chronic limb-threatening ischemia, endovascular, infrapopliteal

Introduction

Chronic limb-threatening ischemia (CLTI) is believed to affect approximately 500 to 1000 per million people in most developed countries.[1] It is also a growing problem in emerging and developing countries due to uncontrolled tobacco use and the increasing worldwide prevalence of diabetes. Traditionally, CLTI has been treated by means of bypass surgery but, in recent years, despite a lack of supporting level I evidence, a growing proportion of affected patients have been offered an endovascular first revascularization strategy.

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The UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA)-funded Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) trial (now known as the BASIL-1 trial) remains the only randomized comparison of a bypass first with an endovascular first revascularization strategy for CLTI secondary to infrainguinal disease.[2] The BASIL-1 trial found that in those patients who survived for more than 2 years after randomization, bypass surgery was associated with a better outcome in terms of overall survival (OS) and amputation-free survival (AFS). However, only around 25% of the patients in BASIL underwent an infrapopliteal (IP) intervention and it is often argued that, given the subsequent advances in endovascular technology and techniques, where BASIL-1 to be repeated, it would probably show a clear advantage for endovascular revascularization over bypass, especially in the IP segment.

In order to address this gap in the evidence base, the UK NIHR HTA-funded BASIL-2 trial is currently randomizing patients with CLTI who require an IP intervention to either an IP vein bypass first or an IP best endovascular therapy first revascularization strategy. The US NIH-funded BEST-CLI trial is also randomizing IP CLTI patients in the United States.

To help define the gray area of equipoise for BASIL-2, we have examined outcomes following IP endovascular intervention in 48 patients randomized in BASIL-1 between 1999 and 2004 and 73 consecutive patients treated a decade later within a UK academic vascular centre between 2009 and 2013 (contemporary series [CS]).

Methods

Individual patient data were obtained from computerized, prospectively gathered BASIL-1 and CS databases. BASIL-1 and CS outcome data were censored at July 1, 2007 and February 1, 2017 respectively, providing a minimum of 3 years follow-up for both cohorts. Contemporary series patients were taken from a computerized database of consecutive endovascular treatments performed for CLTI at a single, UK academic vascular centre. Patients undergoing IP intervention to the same leg during the previous 12 months were excluded. Outcomes compared were AFS, OS, major (above ankle) limb amputation, arterial reintervention, immediate technical success, and length of hospital stay following the index procedure and during the following 12-month period.

Data on primary patency, secondary patency, and restenosis are not presented as these outcomes were not routinely collected during the BASIL-1 trial and nor are they routinely recorded in our unit. Rather, patients undergoing endovascular treatment for CLTI in BASIL-1 and the CS cohorts were offered further imaging and reintervention on the basis of persistent or recurrent signs and symptoms of CLTI. However, Bollinger angiographic scores[3] were used to compare the severity of the disease in both cohorts. Time to event analyses are presented over a 5-year period using Kaplan-Meier plots and hazard ratios (HRs) with 95% confidence intervals (CIs) used to describe treatment effects comparing the CS outcomes with BASIL-1. Differences between the cohorts in other outcomes were compared using the t test, χ^2, or Wilcoxon Rank Sum according to the type and distribution of data. Statistical analysis was performed using SAS version 9.4.

Ethical approval (https://doi.org/10.1186/ISRCTN45398889) was obtained for BASIL-1. Ethical approval was not required for the CS analysis as it involved anonymized data that had been collected as part of routine clinical practice for service evaluation.

Results

The BASIL-1 and CS cohorts were reasonably well-matched in terms of age, sex, previous cerebrovascular disease, diabetes, tissue loss, hypertension, antiplatelet use, and a history of previous arterial intervention (>12 months prior to infrapopliteal endovascular treatment). There were some significant differences in other comorbidities, statin therapy, site and distribution of tissue loss, the pattern of disease, and the extent of disease treated (Tables 1 and 2). A greater proportion of BASIL-1 patients underwent concomitant treatment of the superficial femoral (60% vs 37%, $P = .01$) and above knee popliteal arteries (60% vs 34%, $P = .005$). Bollinger scores were available for 44/48 patients in BASIL and 70/73 patients in CS and overall were very similar (overall score: 94.9 BASIL vs 92.5 CS, $P = .6$). However, BASIL-1 patients had more disease in the femoropopliteal segment (26.4 vs 15.9, $P = .001$) and had less severe disease in the IP segment (68.4 vs 76.6, $P = .03$). Society for Vascular Surgery wound ischemia foot infection scores (WIFi)[4] were unable to be calculated as information regarding the status of infection or size of the wound was not available in the original case report forms or electronic data for either cohort.

Immediate technical success, defined by the operator as successful initial revascularization of the intended target arterial path on postprocedural angiography, was significantly higher in the CS (90% vs 73%, $P = .01$). Technical failure in both cohorts was largely due to an inability to cross the target lesion (21% BASIL-1 vs 5% CS); other reasons given were residual stenosis/recoil, distal embolism, and procedure abandoned at patient request.

Periprocedural morbidity (30 days from intervention) was similar in both groups (13% BASIL-1 and 14% CS). Bleeding complications were low in both cohorts (2% BASIL-1 and 1% CS). However, 2 of the 4 stents placed in the superficial femoral artery (SFA) thrombosed. The median length of stay for the index intervention was significantly shorter in the CS group (5 vs 10 days, $P = .02$). The median number of days spent in hospital over the 12 months following intervention was also fewer in the CS group (13 vs 38, $P = .002$).

There were no significant differences in AFS (HR = 1.00, 95% CI: 0.66-1.54, $P = 1.0$; Figure 1), OS (HR = 1.04, 95% CI: 0.66-1.63, $P = .9$; Figure 2), reintervention (HR = 0.63, 95% CI: 0.31-1.26, $P = .2$; Figure 3), or major (above ankle) amputation (HR = 0.86, 95% CI: 0.38-1.96, $P = .7$; Figure 4) between the two cohorts. At the censor date, 35% BASIL and 30% CS were still alive. Most deaths were cardiovascular (stroke, myocardial infarction, cardiac failure, and sudden

Table 1. Baseline Demographics.

	BASIL Cohort, N = 48	Contemporary Cohort, N = 73	*P* Value
Mean age, years (SD)	77.2 (7.3)	76.9 (10.2)	.8
Male sex (%)	32 (67%)	52 (71%)	.6
Comorbidities			
Mean serum creatinine, mmol/L (SD)	126.6 (68.3), n = 41	125.3 (123.4), n = 73	.9
Stroke/transient ischemic attack (%)	8 (17%)	16 (22%)	.5
Myocardial infarction (%)	14 (29%)	29 (40%)	.2
Angina (%)	10 (21%)	31 (42%)	**.01**
End-stage renal disease (%)	0 (-)	7 (10%)	**.03**
Diabetes mellitus (%)	23 (48%)	45 (62%)	.1
Insulin-dependent diabetes mellitus (%)	8 (35%)	17 (38%)	.7
Clinical presentation			
Tissue loss (%)	41 (85%)	56 (77%)	.2
Site of tissue loss (single patient may have multiple sites)			
Hallux (%)	27 (56%)	24 (33%)	**.02**
Other toes (%)	29 (60%)	21 (29%)	**.001**
Forefoot (%)	10 (21%)	11 (15%)	.4
Hindfoot (%)	7 (15%)	8 (11%)	.5
Ankle (%)	9 (9%)	3 (4%)	**.02**
Above ankle (%)	1 (2%)	14 (19%)	**.01**
Medical therapy			
Antiplatelet agent (%)	30 (63%)	52 (71%)	.3
Dual antiplatelet therapy (%)	3 (6%)	19 (26%)	**.006**
Antihypertensive agent (%)	38 (79%)	58 (79%)	.3
Statin therapy (%)	15 (31%)	50 (68%)	**<.0001**
Formal anticoagulation (warfarin, etc) (%)	9 (19%)	5 (7%)	.05
Previous intervention			
Total (%)	12 (25%)	16 (22%)	.7
Endovascular (%)	7 (15%)	11 (15%)	.9
Surgical (%)	6 (13%)	3 (4%)	.09
Bollinger scores			
Mean total score	94.9	92.5	.6
Mean femoropopliteal segment score	26.4	15.9	**.001**
Mean infrapopliteal segment score	68.4	76.6	**.03**
Mean number of segments scored	12.6/13	12.3/13	.07

Abbreviations: BASIL, Bypass versus Angioplasty in Severe Ischemia of the Leg; SD, standard deviation. *P* values in bold highlight statistical significance (p<.05).

cardiac death; 32% of BASIL-1 patients vs 31% of CS patients, $P = .9$); other common causes of death were pneumonia (23% of BASIL-1 patients vs 18% of CS patients) and malignancy (10% of BASIL-1 patients vs 6% of CS patients). A definitive cause of death could not be established in 29% of BASIL-1 and 23% of CS patients. Although there was no difference in overall reintervention rates, BASIL-1 patients were more likely to be offered secondary vein bypass (16.6% vs 9.6%) while secondary plain balloon angioplasty (PBA) was equally likely (8.3% of BASIL-1 patients vs 9.6% of CS patients).

Discussion

The main finding of the present study is that, despite a significant improvement in immediate technical success, there was no improvement in clinically important, longer term outcomes between BASIL-1 (1999-2004) and CS (2009-2013) patients undergoing primary IP endovascular revascularization. The CS cohort was not part of a randomized controlled trial and therefore patients selected for intervention are prone to selection bias; it is difficult to comment on how many of these patients would have been suitable for both endovascular and open surgical revascularization strategies. This study was not powered to demonstrate significant statistical differences in the primary endpoint; however, the results raise some important questions.

Despite the inherent differences in technology, success of the interventionalist, comorbidities, and availability and use of best medical therapy, it is apparent that from our data patients with predominantly IP disease have poor outcomes in terms of AFS and OS regardless. Survival curves demonstrated for both AFS and OS are almost identical. It appears that patient comorbidity profiles are shifting, patients in the CS tended to have more end-stage renal disease, ischemic heart disease, and higher IP Bollinger scores than those in BASIL-1, this may explain why the improved rates of technical success did not translate into a higher AFS or OS. The proportion of patients in the CS cohort who were unsuitable or unfit for open surgical revascularization is unknown.

Based on this finding, one might argue that given the poor survival in this group of patients that endovascular treatment should be recommended as a first-line treatment in all CLTI

Table 2. Endovascular Procedural Details.

	Number (%)		
	BASIL Cohort, N = 48	Contemporary Cohort (CS), N = 73	*P* Value
Arteries treated			
Superficial femoral	29 (60%)	27 (37%)	**.01**
Above knee popliteal	29 (60%)	25 (34%)	**.005**
Below knee popliteal	28 (58%)	33 (45%)	.2
Tibioperoneal trunk (TPT)	4 (8%)	26 (36%)	**.0007**
Posterior tibial	9 (19%)	16 (22%)	.7
Peroneal	25 (52%)	18 (25%)	**.002**
Anterior tibial	19 (40%)	27 (37%)	.8
Dorsalis pedis	1 (2%)	1 (1%)	.8
Number of IP vessels treated			
TPT most distal target	3 (6%)	18 (25%)	
1 vessel	37 (77%)	49 (67%)	
2 vessels	8 (17%)	6 (8%)	
3 vessels	0 (-)	0 (-)	**.02**
Type of disease treated			
Occlusive	36 (75%)	41 (56%)	**.04**
Stenotic	25 (52%)	50 (68%)	.07
Combination	13 (27%)	18 (25%)	.8
PBA and stent use			
PBA only	47 (98%)	70 (96%)	.1
PBA + Bail out BMS	1 (2%)	4 (5%)	.4
Technical failure			
Inability to cross lesion	10 (76%)	4 (57%)	
Residual stenosis	1 (8%)	1 (14%)	
Embolism	1 (8%)	2 (29%)	
Abandoned at patient request	1 (8%)	0 (-)	
Total technical failure	13/48 (27%)	7/73 (10%)	**.01**

Abbreviations: BASIL, Bypass versus Angioplasty in Severe Ischemia of the Leg; IP, infrapopliteal; PBA, plain balloon angioplasty; TPT, tibioperoneal trunk; BMS, Bare Metal Stent. *P* values in bold highlight statistical significance (p<.05).

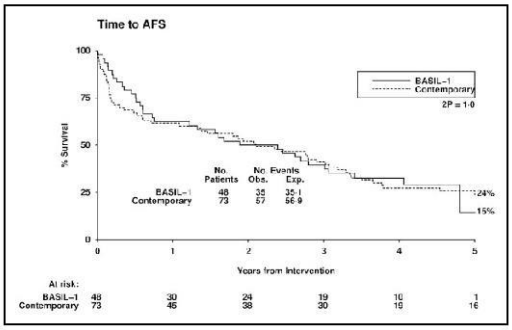


Figure 1. Amputation-free survival.

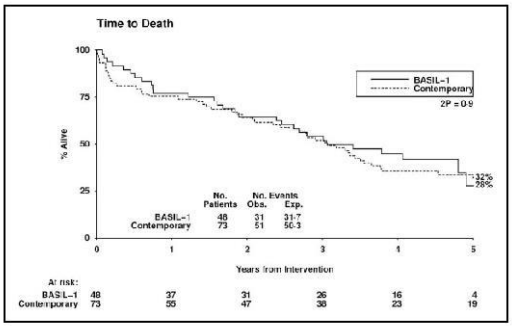


Figure 2. Overall survival.

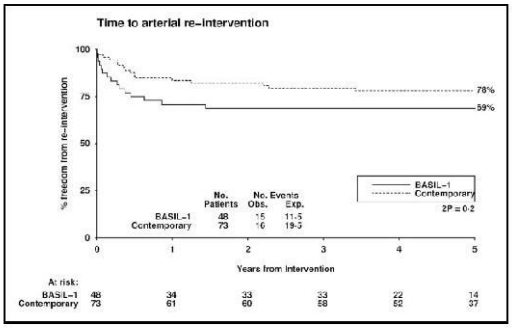


Figure 3. Arterial reintervention.

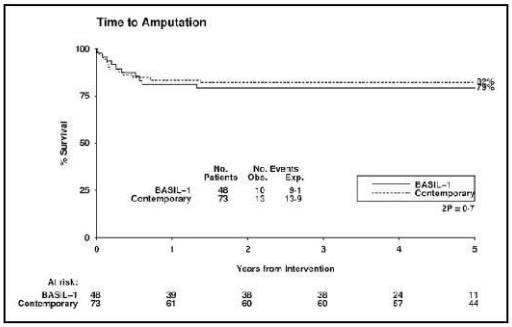


Figure 4. Major amputation.

patients requiring IP intervention given the anticipated increased morbidity associated with surgical bypass. However, we have reported previously that those patients in BASIL-1 who are suitable for both forms of IP revascularization have a significant reduction in ischemic rest pain but similar outcomes in terms of AFS and OS.[5] This was at the expense of somewhat increased periprocedural morbidity and longer length of hospital stay following index admission, but not at 12 months. What is lacking in the literature is high-quality data regarding improvements in patient quality of life, wound healing, and cost-effectiveness; all of which are arguably as important as hard clinical and anatomical end points.

Immediate technical success, as previously described, was measured subjectively by the operator at the time of procedure and was documented when target vessel patency had been achieved angiographically to reflect the methodology of the BASIL-1 trial, making intervention success comparisons equivalent. Patients in the BASIL-1 trial were more likely to undergo concomitant treatment for proximal disease and this may explain the lower rate of technical success. However, one might also expect this to negatively impact longer term outcomes, which was not the case. Contemporary series patients were somewhat more comorbid (although not older) and this may explain why greater technical success did not result in better long-term outcomes. The 90% technical success rate seen in the CS group is comparable to modern standards as reported in a systematic review.[6] Most patients in both cohorts underwent intervention to a single crural vessel. Whether attempting to treat multiple IP vessels results in better outcomes is currently unknown as is the extent to which the use of drug-eluting technologies may have influenced clinical outcomes.

Primarily due to a lack of hospital beds, in the United Kingdom, patients with CLTI are increasingly being managed on an outpatient basis. This probably explains why the CS patients spent fewer days in the hospital. However, whether this is clinically appropriate and cost-effective is an area of considerable controversy. Despite an improvement in the use of the so-called best medical therapy between the BASIL-1 and CS cohorts, there was no improvement in limb salvage or cardiovascular morbidity and mortality. Given the relatively small numbers of patients, this is perhaps not surprising. However, it may also be that patients with CLTI are relatively refractory to medical therapy.

Drug-coated balloons and drug-eluting stents (DES) were not used. Drug technologies did not exist at the time of BASIL-1 and the UK National Institute of Health and Care Excellence recommends against their use on the grounds that there is currently no evidence of clinical and cost-effectiveness in patients with CLTI.[7]

The relevance to the current study of the recently published meta-analysis showing significant excess all-cause mortality with paclitaxel balloons and stents is uncertain.[8] Approximately 90% of the patients within the trials analyzed were treated for intermittent claudication and so there is likely to be a range of views as to whether these data should be extrapolated to CLTI. Both SWEDEPAD and BASIL-3 were paused due to uncertainty regarding such paclitaxel-coated devices.[9] BASIL-3 has now reopened following the advice of the UK MHRA; however, SWEDEPAD 1 and 2 remain closed to recruitment at the time of writing with no reopen date yet agreed. During this time, the use of paclitaxel devices was also excluded from the BASIL-2 trial.[10]

While endovascular options in the IP segment are numerous, current evidence has yet to provide clinical or cost-effectiveness data that suggest PBA should be anything other than the standard of care. Trials comparing drug-eluting balloons (DEB) and PBA initially demonstrated a reduction in restenosis, target lesion revascularization (TLR), and target vessel occlusion at 12-months (anatomical outcomes).[11] Unfortunately, the more recent IN.PACT DEEP trial revealed a higher rate of major amputation compared to control (PBA).[12] Pooled data comparing DES has suggested more promising results. Katsanos et al reported reduced restenosis, TLR, amputation, and improved wound healing when compared to control (Bare Metal Stent or PBA), without any impact on mortality.[13] These findings have been corroborated,[14] however, most would agree that trial numbers are small in selected centers and selected lesions and further clinical evidence is clearly required, particularly in regard to DEB.

BASIL-1 remains only published randomized controlled trial comparing bypass and endovascular intervention for CLTI and showed that, for most patients, vein bypass is associated with a better outcome in terms of AFS and OS. Those who choose to ignore this sole source of level 1 evidence often justify their practice by arguing that, given the advances in endovascular techniques and technologies, it is obvious that if BASIL-1 were to be repeated then it would show that an endovascular first revascularization strategy is the preferred option for most, perhaps all, CLTI. However, as the present data once again demonstrate, this is an argument in search of some evidence to support it. Indeed, what data we have from BASIL-1 and other sources[5] suggest that IP endovascular therapy should probably be reserved for those patients who cannot undergo vein bypass.

Conclusions

In summary, therefore, despite a significant improvement in the immediate technical angiographic success of IP PBA between 1999-2004 and 2009-2013, there were no significant improvements in longer term limb and mortality-based end points. Patients in both cohorts had poor outcomes and this could possibly be explained by a shift in comorbidity profile over the last decade. Results from the on-going BASIL-2 and BEST-CLI randomized controlled trials are required in order to properly define the clinical and cost-effectiveness of endovascular intervention in patients with CLTI due to IP disease which has been recognized by key peripheral arterial disease expert groups worldwide.[7,15,16]

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The BASIL-1 trial was funded by UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA), a UK government body.

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Vascular and Endovascular Surgery
2021, Vol. 55(1) 26-32
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DOI: 10.1177/1538574420953949
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Comparison of Clinical Outcomes in Patients Selected for Infra-Popliteal Bypass or Plain Balloon Angioplasty for Chronic Limb Threatening Ischemia Between 2009 and 2013

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Abstract

Introduction: A published subgroup analysis of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial suggests that, in patients with chronic limb threatening ischemia (CLTI) due to infra-popliteal (IP) disease, clinical outcomes are better following vein bypass surgery (BS) than after plain balloon angioplasty (PBA). The aim of the present study is to determine if clinical outcomes following IP revascularization in our unit are concordant with those found in BASIL-1. **Methods:** We analyzed prospectively gathered data pertaining to 137 consecutive CLTI patients undergoing IP PBA or BS between 2009 and 2013. We compared 30-day morbidity and mortality, days in hospital (index admission and out to 12-months), amputation free survival (AFS), overall survival (OS), limb salvage (LS), and freedom from arterial re-intervention (FFR). Patient outcomes were censored on 1 February 2017, providing a minimum 3 years follow-up. **Results:** Patients undergoing BS (73/137, 47%) tended to be younger, have less comorbidity, and were more likely to be on best medical therapy (BMT). BS patients spent more days in hospital during the index admission (median 9 vs 5, $p = .003$), but not out to 12 months (median 15 vs 13, NS). BS patients suffered more 30-day morbidity (36% vs 10%, $p < .001$), mainly due to infective complications, but not mortality (3.1% vs 6.8%, NS). AFS ($p = .001$) and OS ($p < .001$), but not LS or FFR, were better after BS. **Conclusions:** CLTI patients selected for revascularization by means of IP BS had better long-term outcomes in terms of AFS and OS, but not FFR or LS. Although we await the results of the BASIL-2 trial, current data support the BASIL-1 sub-group analysis which suggests that patients requiring revascularization for IP disease should have BS where possible and that PBA should usually be reserved for patients who are not suitable for BS.

Keywords

chronic limb threatening ischemia, endovascular, bypass surgery, infrapopliteal, tibial

Introduction

Chronic limb threatening ischemia (CLTI) is a growing global health and social care problem due to widespread tobacco use and the increasing worldwide prevalence of diabetes.[1,2] The condition remains associated with very poor outcomes in terms of major lower limb amputation (MLLA) and premature cardiovascular and all-cause mortality. The evidence base underpinning the management of CLTI is limited, especially with regard to revascularization strategies, and particularly with regard to the infra-popliteal (IP) segment. The UK National Institute of Health Research (NIHR) Health Technology Assessment (HTA)-funded Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 remains the only published randomized controlled trial (RCT) to have compared infra-inguinal bypass surgery (BS) with plain balloon angioplasty (PBA) for CLTI.[3]

In 2017, we published a BASIL-1 IP sub-group analysis that demonstrated a trend toward improved amputation free survival (AFS) and overall survival (OS) in those undergoing BS, and showed that BS was associated with highly significantly better quality of revascularization than PBA in terms of relief of ischemic rest pain.[4] However, the procedures were performed between 1999 and 2003 leading to suggestions that

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BASIL-1 outcomes are no longer relevant to current endovascular practice.

To further address the issue of preferred IP revascularization strategies for CLTI, the UK NIHR HTA funded the BASIL-2 trial which compares IP vein BS with best endovascular treatment (BET) in patients presenting with CLTI who require IP revascularization.[5] Although the BASIL-2 trial is likely to complete recruitment in 2020, there then follows a minimum of 2 years of follow-up, such that the final results are unlikely to be published until early 2023. In the meantime, therefore, there remains a large "gray area of clinical equipoise" regarding IP revascularization strategies for CLTI.

The aim of the present study was to determine if important clinical outcomes following IP revascularization in our unit (2009-2013) are concordant with those found in BASIL-1 (2009-2013) and, further, to encourage participation in BASIL-2.

Methods

This was a retrospective analysis of prospectively gathered hospital data pertaining to 137 consecutive CLTI patients selected for either IP PBA or BS in our unit between 1 June 2009 and 30 July 2013. Prior to revascularization, all patients were discussed in a vascular multi-disciplinary meeting. Intervention was planned based on the availability of venous conduit, patient fitness, patient choice and the technical options following detailed imaging. We compared 30-day morbidity and mortality, length of hospital stay (for both index admission and out to 12-months), amputation free survival (AFS), overall survival (OS), limb salvage (LS), and freedom from arterial re-intervention (FFR). In addition to this, we compared AFS and OS in those that survived the primary hospital episode with the index limb intact.

As the data analyzed were collected as part of normal routine clinical practice, ethical approval was not sought in accordance with advice from the UK National Research Ethics Service (http://www.hra-decisiontools.org.uk/ethics/). Patient outcomes were censored on 1 February 2017 so providing a minimum of 3 years follow-up. Continuous data are reported using mean or median values and compared using t-test or Mann-Whitney U test, depending on the characteristics of data distribution. Categorical data are compared using Fishers Exact or Chi-squared test. Time to event data were analyzed using the Kaplan-Meier method and log-rank statistics presented as a hazard ratios (HR) and 95% confidence intervals (CI). Statistical analysis was performed using R version 3.6.1 (2019-07-05)© 2019. The R Foundation for Statistical Computing. Graphical illustrations presented were prepared using GraphPad Prism 8 software ver. 8.3.0, GraphPad Software, LLC©.

Results

Patients undergoing BS (64/137, 47%) tended to be younger with less co-morbidity and were also more likely to be on best medical therapy (BMT) (Table 1). Patients undergoing PBA had a higher incidence of previous myocardial infarction (BS 10/64, 16% vs. PBA 29/73, 40%, p = .004) and were more likely to have diabetes (BS 27/64, 42% vs. PBA 45/73, 62%, p = .02). Although the number of patients with tissue loss in both groups was similar, the PBA patients tended to have more hindfoot involvement. A higher proportion of patients undergoing BS had undergone previous intervention in the index leg (BS 24/64, 38% vs. PBA 16/73, 22%, p = .04).

Table 1. Baseline Characteristics.

	BS (n = 64)	PBA (n = 73)	p value
Mean and SD age (years)	73.2 (11.2)	76.9 (10.2)	0.02
Male (%)	48 (75%)	52 (71%)	NS
Comorbidities			
Mean serum creatinine mmol/l (SD)	103.7 (112.5)	125.3 (123.4)	NS
Stroke / Transient Ischemic Attack (%)	13 (20%)	16 (22%)	NS
Myocardial Infarction (%)	10 (16%)	29 (40%)	0.004
Angina (%)	17 (27%)	31 (42%)	0.05
End stage renal disease (%)	2 (3%)	7 (10%)	NS
Diabetes Mellitus (%)	27 (42%)	45 (62%)	0.02
Insulin dependent Diabetes Mellitus (%)	10/27 (37%)	17/45 (38%)	NS
Clinical Presentation			
Tissue loss (%)	44 (69%)	56 (77%)	NS
Site of tissue loss (single patient may have multiple sites)			
Hallux (%)	19 (30%)	24 (33%)	NS
Other toes (%)	19 (30%)	21 (29%)	NS
Forefoot (%)	6 (9%)	11 (15%)	NS
Hindfoot (%)	1 (2%)	8 (11%)	0.03
Ankle (%)	3 (5%)	3 (4%)	NS
Above ankle (%)	10 16%)	14 (19%)	NS
Medical therapy			
Antiplatelet agent (%)	55 (86%)	52 (71%)	0.04
Dual antiplatelet therapy (%)	8 (13%)	19 (26%)	0.04
Antihypertensive agent (%)	51 (80%)	58 (79%)	NS
Statin therapy (%)	57 (89%)	50 (68%)	0.004
Anticoagulation (%)	13 (20%)	5 (7%)	0.02
Previous Intervention			
Total (%)	24 (38%)	16 (22%)	0.04
Endovascular (%)	17 (27%)	11 (15%)	NS
Surgical (%)	10 (17%)	3 (4%)	0.03

In those patients undergoing PBA, 4 also received a bare metal stent (BMS). No drug coated balloons (DCB) or drug eluting stents (DES) were used. Only 6 PBA patients had more than one crural vessel treated (Table 2). Immediate technical success (defined by the operator at the time of procedure) was 90%. In 4 cases it was not possible to cross the target lesion; 2 patients had distal embolism which resulted in loss of the target vessel; and 1 patient had a residual stenosis that was not amenable to stenting.

The majority of patients undergoing BS had great saphenous venous conduit (53/64, 83%) which was usually reversed (Table 3). Prosthetic material was used in 9 patients (3 prosthetic and 6 composite-sequential grafts). Immediate technical success was 97%; 2 procedures were abandoned as the target

Table 2. PBA Treatment Details.

		No. (n = 73)
Arteries treated	Superficial Femoral	27 (37%)
	Above Knee Popliteal	25 (34%)
	Below Knee Popliteal	33 (45%)
	Tibio-peroneal Trunk	26 (36%)
	Posterior Tibial	16 (22%)
	Peroneal	18 (25%)
	Anterior Tibial	27 (37%)
	Dorsalis Pedis	1 (1%)
Number of IP vessels treated	TPT most distal target	18 (25%)
	1 vessel	49 (67%)
	2 vessels	6 (8%)
	3 vessels	0 (-)
Type of disease treated	Occlusive	41 (56%)
	Stenotic	50 (68%)
	Combination	18 (25%)
Type of intervention	PBA	70 (96%)
	PBA + bare metal stent	4 (5%)
Technical Failure	Inability to cross lesion	4/7 (57%)
	Residual stenosis	1/7 (14%)
	Embolism	2/7 (29%)
	Abandoned at patient request	0 (-)
	Total technical failure	7/73 (10%)

Table 3. BS Treatment Details.

		No. (n = 64)
Conduit	Reversed vein (when vein used alone)	34 (53%)
	Non-reversed vein (when vein used alone)	19 (30%)
	Leg vein	46 (72%) Ipsilateral GSV 6 (9%) contralateral GSV
	Arm vein	1 (2%)
	Prosthetic	3 (5%)
	Composite Sequential	6 (9%)
	No bypass performed as distal target not patent	2 (3%)
Proximal anastomosis	Common femoral artery	51 (80%)
	Superficial femoral artery	5 (8%)
	Profunda femoris artery	0 (-)
	Above knee popliteal artery	4 (6%)
	Below knee popliteal artery	1 (2%)
Distal anastomosis	Tibioperoneal trunk	8 (12%)
	Posterior tibial artery 1/3	16 (25%)
	Posterior tibial artery 2/3	4 (6%)
	Posterior tibial artery 3/3	6 (9%)
	Peroneal artery 1/3	12 (19%)
	Peroneal artery 2/3	0 (-)
	Peroneal artery 3/3	2 (3%)
	Anterior tibial artery 1/3	9 (14%)
	Anterior tibial artery 2/3	2 (3%)
	Anterior tibial artery 3/3	1 (2%)
	Dorsalis pedis	2 (3%)
Technical failures	Early failure (<30 days)	5 (8%)
	Abandoned, no outflow vessel	2 (3%)
	Total technical failure	7/64 (11%)

crural vessel was judged unsuitable for bypass following surgical exposure. In 5 patients, the bypass failed within 30 days.

Thirty-day mortality was non-significantly worse in patients undergoing PBA (RR 2.19, 95% CI 0.44-10.91, 5 patients, 6.8% vs. 2 patients, 3.1% BS, NS). In both cohorts the most common causes of death were pneumonia, sepsis from other causes and cardiac disease (Table 4). Those selected for BS suffered more 30-day morbidity (RR 3.75, 95% CI 1.72-8.15, $p < .001$), mainly as a result of surgical site infection (SSI) and other causes of sepsis (**Table 5**). BS patients spent more days in hospital during the index admission (median 9 vs 5 days, $p = .003$), but not out to 12 months (median 15 vs 13 days, NS).

AFS was significantly better in those selected for BS (HR 0.50, 95% CI 0.33-0.76, $p = .001$, Figure 1). AFS after BS was estimated at 69%, 58% and 56% at 1, 3 and 5 years respectively and the mean AFS after BS was 4.6 (3.8 to 5.5, 95% CI) years. AFS after PBA was estimated at 62%, 42% and 26% at the same time points and the mean AFS after PBA was 2.8 (2.2 to 3.4, 95% CI) years.

OS was also significantly better in those selected for BS (HR 0.42, 95% CI 0.27-0.66, $p < .001$, Figure 2). OS following BS was estimated at 80%, 71% and 69% at 1, 3 and 5 years respectively, and the mean OS after BS was 5.6 (4.7 to 6.4, 95% CI) years. OS following PBA was estimated at 75%, 52% and 34% at the same time points, and the mean OS after PBA was 3.5 (2.9 to 4.1, 95% CI) years.

There was no significant difference in LS between BS and PBA (HR 0.80, 95% CI 0.35-1.81, $p = .6$, Figure 3). In the BS group, 6 patients had transtibial and 4 had transfemoral amputations. In comparison, 7 of those undergoing PBA required transtibial and 4 had transfemoral amputations.

Table 4. Cause of Death.

Cause	BS (n = 64)	PBA (n = 73)	p value
Pneumonia/Respiratory	4 (6%)	10 (14%)	NS
Sepsis (other causes)	2 (3%)	4 (5%)	NS
Malignancy	2 (3%)	3 (4%)	NS
Cardiac	3 (5%)	9 (12%)	NS
Acute Kidney Injury	2 (3%)	0 (-)	NS
Unknown	8 (13%)	16 (22%)	NS
Stroke	2 (3%)	4 (5%)	NS
Upper Gastrointestinal bleeding	1 (2%)	0 (-)	NS
"Old age"	0 (-)	2 (3%)	NS
Intracranial bleed	0 (-)	2 (3%)	NS
Venous thromboembolism	0 (-)	1 (1%)	NS
Total	**24/64 (38%)**	**51/73 (70%)**	**<.001**

There was no significant difference in FFR between BS and PBA (HR 0.99, 95% CI 0.48-2.05, $p = 1.0$, **Figure 4**). Eight patients (12.5%) in the BS group required secondary bypass, and 3 (4.7%) went on to have PBA. Seven of those undergoing

Table 5. Peri-Procedural (Thirty-Day) Morbidity.

Cause	BS (n = 64)	PBA (n = 73)	p value
Bleeding	3 (5%) (1 CD IIIb)	1 (1%) (CD II)	NS
Sepsis (urine, chest)	7 (11%) (CD II)	0 (-%)	.004
Surgical site infection (SSI)	9 (14%) (6 CD II, 3 CD IIIb)	0 (-%)	<.001
Myocardial infarction / congestive cardiac failure	3 (5%) (2 CD II), 1CD V)	4 (5%) (1 CD II, 3CD V)	NS
Groin haematoma	3 (5%) (CD IIIb)	0 (-)	NS
Venous thromboembolism	1 (2%) (CD II)	2 (3%) (1/2 CD II) (1/2 CD V)	NS
Total	23/64 (36%)	7/73 (10%)	<.001

Abbreviations; CD, Clavien-Dindo.[16]

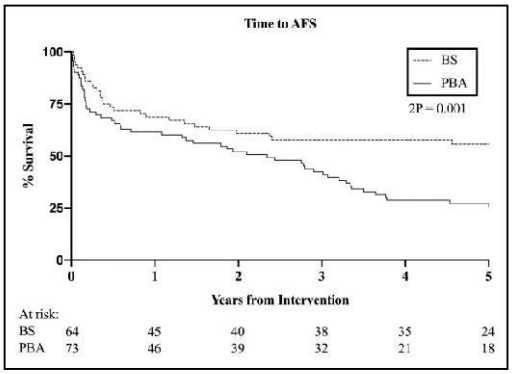


Figure 1. Amputation free survival. HR 0.50, 95% CI 0.33-0.77, p = .001.

PBA (9.6%) had repeat PBA, and 7 patients (9.6%) went on to have BS.

Overall, 63 and 66 patients undergoing BS and PBA respectively were discharged alive from our unit without undergoing transtibial or transfemoral amputation. Of these patients, those undergoing BS had significantly better AFS (HR 0.54, 95% CI 0.35-0.84, p = .006) and OS (HR 0.46, 95% CI 0.29-0.74, p = .002) than those undergoing PBA.

Discussion

The main finding of the present study is that important clinical outcomes following IP BS and PBA in a non-randomized contemporary series of patients treated in our unit between 2009 and 2013 are very similar, both in absolute and relative terms, to those reported in patients recruited to the multi-centre

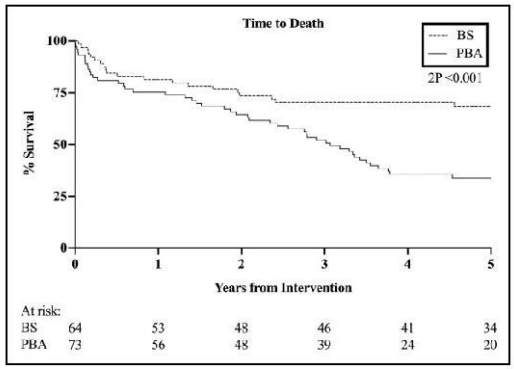


Figure 2. Overall survival. HR 0.42, 95% CI 0.27-0.66, p < .001.

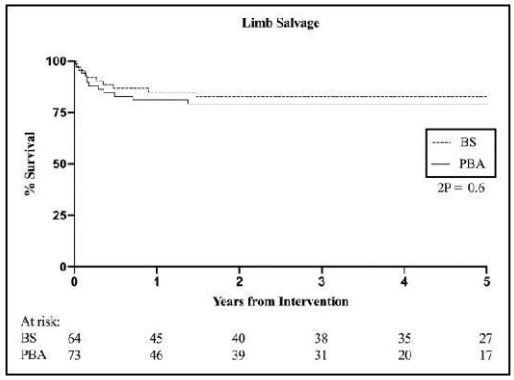


Figure 3. Limb salvage. HR 0.8, 95% CI 0.35-1.81, p = .6.

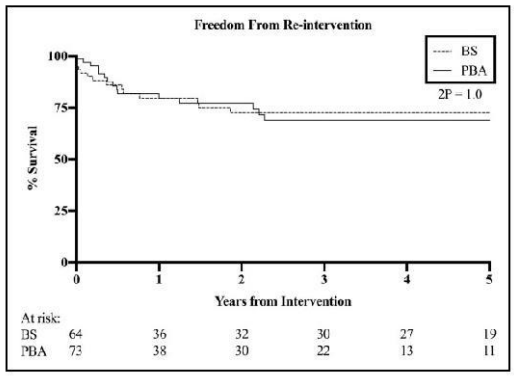


Figure 4. Freedom from re-intervention. HR 0.99, 95% CI 0.48-2.05, p = 1.0.

BASIL-1 RCT between 1999 and 2003. In our series, patients undergoing BS did significantly better in terms of AFS and OS than those receiving PBA. BASIL-1 reported similar outcomes but to a smaller degree of significance than we present here.

Patients in this contemporary series (CS) selected for BS were similar in terms of age and co-morbidity (previous cerebrovascular disease, myocardial infarction, end stage renal disease [ESRD] and diabetes) to those patients in the BASIL-1 IP subgroup (B1). However, those undergoing PBA tended to have a higher burden of such co-morbidity.

One may argue that the number of IP revascularizations in a 50-month period is low, given the size of our vascular unit. In the last decade we have seen a shift in the presentation of disease. A prospective cohort study performed in our unit between 2014 to 2018 to showed, disappointingly, that around 40% of patients who present with CLTI with significant IP disease are either too unfit for any intervention, present with a non-salvageable limb, or have pattern of disease that is not amenable either endovascular intervention or BS. The reasons for this are probably increasing burden of diabetes, ESRD, and advancing age of the general and CLTI population.

In terms of BMT, the prescription of statins in the current BS cohort had more than doubled when compared to the B1 BS patients (B1 39% vs. CS 89%). In the B1 subgroup, 75% of patients undergoing BS were prescribed an antiplatelet agent; in the current BS cohort this was somewhat higher at 86%. Although improved rates of statin prescription were also seen in the current PBA cohort compared with the B1 PBA patients (68% vs 25%), rates were still much lower than in those undergoing BS. Only 58% of patients undergoing PBA in the B1 cohort were prescribed an antiplatelet agent. Although this had increased to 71% in our current cohort, this is still far from optimal and may have contributed to the poorer outcomes in this group. More rigorous follow up in the BS group (graft surveillance) provides an additional opportunity to reinforce the importance of BMT. Reduced outpatient contacts with the patients undergoing PBA may explain the difference in statin prescribing practice. The recorded increase in statin prescription is likely due to an increased awareness of the importance of BMT in the CLTI population. This was further reinforced in 2012 by the National Institute of Health and Care Excellence (NICE) Clinical Guideline (CG 1457) on peripheral arterial disease.[6]

Disappointingly, the majority of CLTI patients (>80%) still present with tissue loss and this has remained unchanged since B1. It is difficult to know if the extent of tissue loss was different between these groups as the Society for Vascular Surgery (SVS) Wound Ischaemia Foot Infection (WIfI)[7] tool was not in use during either study period. However, patients in the current PBA group tended to more tissue loss in the hindfoot, which may have contributed to their overall poorer outcomes.

We have previously reported a comparison of outcomes in the patients undergoing IP PBA in this cohort with similar patients in the B1 subgroup.[8] In that study we demonstrated that, although patients were similar at baseline, patients undergoing IP intervention had a greater burden of FP disease in patients from the B1 cohort. Although PBA technical success was also somewhat better in our current IP cohort than B1, this did not appear to translate into any longer-term clinical benefit in terms of AFS or OS.

Immediate technical success rates have improved since BASIL-1 for both BS (97% vs 86%) and PBA (90% vs. 73%). Our current technical success for patients undergoing IP PBA is comparable to results published in the literature.[9] This may be due to improved technologies, techniques and better patient selection.

Following PBA, 7 patients (9.6%) went on to have salvage vein BS. One may argue that this group of patients would have been better served with primary vein BS. However, how this would have affected outcomes is a matter of speculation. It is hoped that the results of the BASIL-2 trial[5] will aide decision making in this group of patients.

Patients in our current series spent less time in hospital than those a decade previously in B1. The length of index hospital admission was almost 50% lower in our recent cohort when compared to B1 (median BS 18 days vs. PBA 10 days) for both the BS and PBA groups. B1 patients also spent longer in hospital over the 12-months following intervention (a median of over 40 days).

AFS in B1 was estimated at 36% for BS and 15% for PBA out to 5 years. This was higher in our current series (BS 56% vs. PBA 25%). Trends in OS significantly improved in those undergoing BS (B1 49% vs. CS 68%) but not PBA (B1 28% vs. CS 32%) at the same time point. Although this is likely to be multifactorial, as discussed above, it may be due in part to the better use of BMT seen in our current series. In those that survived, LS (approximately 80%) and FFR (approximately 70%) were similar to that observed for both BS and PBA in B1.

Interestingly, after removing from the analysis those patients that did not survive or underwent amputation during the index hospital admission, the significant differences in favor of BS in terms of AFS and OS remained unchanged. As in BASIL-1, these differences were most pronounced after 2 years from index intervention.

Peri-procedural (thirty-day) morbidity in the current series was very similar to that reported in B1. Thus, in the B1 BS group, 36% experienced a complication within 30-days and the majority of these were SSI and other forms of sepsis.

Unlike B1, the current cohort of patients was not randomised and so there will have been selection bias regarding the choice of revascularization. However, what the data do show is that, if a patient was deemed fit enough for BS, then long-term AFS and OS were significantly better than after PBA. This supports the findings of the BASIL-1 trial overall[10] and the BASIL-1 IP subgroup analysis.[8] The unanswered question is how many patients who underwent PBA in the current cohort could, and perhaps should, have undergone BS instead; and, if they had, would they have enjoyed a better longer-term outcome. Only randomised controlled trials, such as BASIL-2, that are free of selection basis can address these types of questions.

Use of drug coated balloons and drug eluting stents were not considered UK standard of care during the time of the study

as there was no evidence of clinical and, in particular, cost-effectiveness.[6] The UK NICE was criticized for this stance at the time but, more recently, significant controversy has surrounded the use of such devices owing to meta-analyses[11,12] demonstrating an increase in all-cause mortality with paclitaxel devices. Following the publication of these data, paclitaxel-based devices were excluded from BASIL-2[5] and recruitment was paused in both the BASIL-3 trial[13] and SWEDEPAD[14] trials. BASIL-3 re-opened in September 2019 and is nearing the end of recruitment. However, at the time of writing, both SWEDEPAD registry trials remain closed.

The recently published Global Vascular Guidelines[1,2] recommend an individually tailored approach to revascularization in patients with CLTI. BS is recommended for infrainguinal disease in average risk patients with a suitable venous conduit (expected peri-operative mortality of less than 5% or life expectancy >2 years). However, these recommendations are based on the current best available evidence which is categorised by the GVG writing group as "Level C" (low). Going forward, it is very important that clinicians offer patients evidence-based revascularization (EBR) that is both clinically and, very importantly, given that the greatest future CLTI burden is likely to be in low- and middle-income countries, cost effective. The results of the BASIL-2[5], BASIL-3[13] and BEST-CLI[15] randomized controlled trials are eagerly awaited.

In conclusion, in CLTI patients selected for IP revascularization at our unit, PBA was associated significantly poorer AFS and OS when compared to BS. This may be explained, at least in part, by the higher prevalence of diabetes and ischemic heart disease in this group. However, patients undergoing BS had high peri-procedural morbidity and increased length of stay. Overall, clinical outcomes in the current cohort were very similar to those reported in BASIL-1, current patients undergoing BS fared somewhat better than those undergoing PBA. Current data support the BASIL-1 IP subgroup analysis and once again suggest that CLTI patients requiring revascularization for IP disease should have BS where possible; and that PBA should usually be reserved for patients who are not suitable for BS.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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Procedural and 12-month in-hospital costs of primary infra-popliteal bypass surgery, infra-popliteal best endovascular treatment, and major lower limb amputation for chronic limb threatening ischemia

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ABSTRACT

Objective: Chronic limb-threatening ischemia (CLTI) is a growing global problem due to the widespread use of tobacco and increasing prevalence of diabetes. Although the financial consequences are considerable, few studies have compared the relative cost-effectiveness of different CLTI management strategies. The Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL)-2 trial is randomizing patients with CLTI to primary infra-popliteal (IP) vein bypass surgery (BS) or best endovascular treatment (BET) and includes a comprehensive within-trial cost-utility analysis. The aim of this study is to compare over a 12-month time horizon, the costs of primary IP BS, IP best endovascular treatment (BET), and major limb major amputation (MLLA) to inform the BASIL-2 cost-utility analysis.

Methods: We compared procedural human resource (HR) costs and total in-hospital costs for the index admission, and over the following 12-months, in 60 consecutive patients undergoing primary IP BS (n = 20), IP BET (n = 20), or MLLA (10 transfemoral and 10 transtibial) for CLTI within the BASIL prospective cohort study.

Results: Procedural HR costs were greatest for BS (BS £2551; 95% confidence interval [CI], £1934-£2807 vs MLLA £1130; 95% CI, £1046-£1297 vs BET £329; 95% CI, £242-£390; $P < .001$, Kruskal-Wallis) due to longer procedure duration and greater staff requirement. With regard to the index admission, MLLA was the most expensive due to longer hospital stay (MLLA £13,320; 95% CI, £8986-£18,616 vs BS £8714; 95% CI, £6097-£11,973 vs BET £4813; 95% CI, £3529-£6097; $P < .001$, Kruskal-Wallis). The total cost of the index admission and in-hospital care over the following 12 months remained least for BET (MLLA £26,327; 95% CI, £17,653-£30,458 vs BS £20,401; 95% CI, £12,071-£23,926 vs BET £12,298; 95% CI, £6961-£15,439; $P < .001$, Kruskal-Wallis).

Conclusions: Over a 12-month time horizon, MLLA and IP BS are more expensive than IP BET in terms of procedural HR costs and total in-hospital costs. These economic data, together with quality of life data from BASIL-2, will inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies within the BASIL-2 cost-utility analysis. (J Vasc Surg 2021;■:1-10.)

Keywords: Amputation; Chronic limb-threatening ischemia; Costing; Endovascular; Surgery

Chronic limb threatening ischemia (CLTI)[1] is an increasing global health and social care problem due to widespread tobacco use and the growing prevalence of diabetes. Patients usually present with complex, multi-level disease that increasingly involves the infra-popliteal (IP) arteries. The financial consequences of this growing CLTI burden are considerable, especially for low- and middle-income countries.[1,2] In the United Kingdom (UK), the total annual direct health care cost of caring for patients with CLTI has been estimated at £200 million, but this is likely to be a significant underestimate of the true overall financial burden of the disease.[3] In the United States (U.S.), this figure is estimated to be in the range of $10 to $20 billion U.S.[4] The annual cost of revascularization for CLTI in the U.S. has been estimated at $4.2 billion U.S. per year, with an additional $625 million U.S. spent on unplanned readmissions in the 30 days following intervention.[5] The cost of a CLTI admission in the U.S. has been estimated at around $23,000 U.S.[6] Evidence suggests that all these costs are increasing rapidly.[7] Despite this, there are surprisingly few published studies that have examined the

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The BASIL-2 Trial is funded by the United Kingdom National Institute for Health Research Health Technology Assessment.

Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

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https://doi.org/10.1016/j.jvs.2021.07.232

relative costs and cost-effectiveness of the three main primary interventions for CLTI: bypass surgery (BS), best endovascular treatment (BET), and major lower limb amputation (MLLA). This is perhaps because of the difficulty of accurately estimating the true cost of each component of care in the context of a complex patient journey that often involves repeated readmissions and further procedures, as well as community care, over several years.[8,9]

In the UK Bypass vs Angioplasty in Severe Ischaemia of the Leg (BASIL)-1 trial, the mean overall hospital costs in the 12 months following randomization were significantly higher after BS ($34,378 U.S.) than plain balloon angioplasty (PBA) ($25,909 U.S.).[9] However, due to more hospital admissions and further procedures after PBA, the cost difference reduced to $5000 U.S. at 3 years (bypass $45,322 vs PBA $39,801) and was not significant. Even fewer economic data are available for patients with CLTI undergoing MLLA. One study estimated the in-patient cost at around $40K U.S. based on a median stay of 9 days.[10] The only published study of long-term costs following primary MLLA for CLTI suggests it is around $80K U.S. over 10 years.[11] However, estimating long-term costs is challenging given the poor overall survival (OS) of this group.[12]

The UK BASIL-2 trial is randomizing patients with CLTI between primary IP vein bypass (VB) and BET, which in the UK is predominantly PBA, and incorporates a comprehensive cost-utility health economic analysis.[13,14] The BASIL prospective cohort study (PCS) is running alongside the main trial and comprises all patients with CLTI admitted to The Heart of England Foundation Trust, University Hospitals Birmingham (HEFT UHB) vascular unit between July 2014 and September 2018. The aim of the present study is to calculate and compare, over a 12-month time horizon, the costs of primary IP BS, IP BET, and MLLA in patients enrolled in the BASIL PCS in terms of human and hospital-based resource utilization in order to inform the BASIL-2 health economic analyses.

METHODS

Patients provided informed, written consent (National Research Ethics Service, Coventry & Warwick, ref: 14/WM/0057). All patients who were admitted to the HEFT UHB as an emergency (non-elective, unplanned admission) with CLTI (as defined by the Global Vascular Gudelines[1,2]) were considered. Only patients with significant peripheral arterial disease that would require revascularization to vessels distal to, and including, the tibioperoneal trunk were recruited. We compared procedural human resource (HR) costs and in-hospital costs for the index admission and over the following 12 months in 60 consecutive patients undergoing primary IP BS (n = 20), IP BET (n = 20), or MLLA (10 transfemoral and 10 transtibial) for CLTI. Patients were studied clinically for 12 months after discharge from their index admission using prospectively routinely gathered hospital data. Patients were described in terms of baseline demographics and Wound Ischemia Foot infection (WIFi) clinical grade to quantify the disease burden of CLTI.[13] Amputation-free survival (AFS) and OS were also estimated for each cohort.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center prospective observational study
- **Key Findings:** In 60 patients undergoing treatment for chronic limb-threatening ischemia, bypass surgery (BS) and major lower limb amputation (MLLA) were significantly more expensive than best endovascular treatment (BET) in terms of human resources (BS £2551 vs MLLA £1130 vs BET £329) and in-hospital costs (MLLA £13,320 vs BS £8714 vs BET £4813).
- **Take Home Message:** In terms of calculated procedural human resource and in-hospital costs, both infra-popliteal vein bypass and MLLA are more expensive than infra-popliteal plain balloon angioplasty. These data together with quality-adjusted life-year data from BASIL-2 will help inform the calculation of incremental cost-effectiveness ratios for different chronic limb-threatening ischemia management strategies.

HEFT UHB, UK. Our hospital is the hub of a vascular network that takes referrals and manages patients with vascular disease from three other local, "spoke" institutions. This covers a population base of over 1.2 million patients. At the time of study, the unit was staffed by 6 vascular surgery consultants. There were 24 dedicated inpatient beds and 4 high-dependency beds for patients with vascular disease on the vascular ward. The majority of patients with tissue loss secondary to CLTI are admitted as an emergency from either the outpatient clinic, emergency department, or surgical assessment unit. We endeavor to adhere to practice guidelines delineating which patients with CLTI should be managed on an inpatient or outpatient basis as prescribed by the Vascular Society of Great Britain and Ireland.[14] We have access to an elective, dedicated vascular operating list for eight sessions per week (four full days, 8am to 5pm) and an emergency theater (24 hours), which is shared between all surgical specialties. At the time of study, our hybrid theater was not yet commissioned. Interventional radiology access was available from Monday to Friday, 8am to 5pm.

Procedural HR micro-costing. Procedural HR data were collected for each primary intervention from arrival at, to discharge from, the operating theater or

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interventional suite. The lead author (M.P.) attended at the end of each procedure and recorded to the nearest minute the presence of all staff involved. This information was later cross-referenced with theater and interventional radiology electronic records to ensure accuracy. Staff costs (UK£ per/hour [p/h]) were obtained from the Personal Social Services Research Unit (PSSRU) (2018).[15] Junior medical staff were assumed to be working a 48-hour working week unless otherwise stated.

The PSSRU 2018 document "Unit Costs of Health and Social Care[15] delineates the average hourly rates of National Health Service (NHS) staff (dependent on grade). Consultant grade doctors (surgeon/anesthetist/interventional radiologists) cost the NHS £108 p/h. The cost of other hospital-based doctors ranges from £24 to £105 p/h depending on grade, based on a 56-hour working week. Hospital-based nurses, operating department practitioners, and radiographers all operate under a banding system in the UK NHS system (from 1 to 9) that attracts pay between £28 and £123 p/h.

To calculate median costs, exact hourly rates for the type and grade of personnel present were calculated and multiplied by the time, to the nearest minute, that each individual spent at each phase of a procedure. These costs were then combined for each procedure to give the total HR cost for IP BS, BET, and MLLA.

Patient-level analysis of in-hospital costs. NHS Index Reference Costs (2014/15)[16] were calculated prospectively from patient level data pertaining to the following:

- Index intervention
- Index hospital admission: costs for days in hospital were separated into those spent in the ward, high-dependency unit and intensive care unit settings
- Further admissions in the 12 months following discharge from the index admission
- Further interventions not requiring admission; for example, "day case" BET
- Outpatient appointments
- Investigations required for diagnosis, treatment, and ongoing surveillance
- Reinterventions (during the hospital admission and within the following 12 months); any morbidity was described in terms of Clavien-Dindo grade.[17]

Costs pertaining to individual instrumentation, endovascular devices, wires, or catheters were not included in this analysis. The term 'in-hospital costs' refers to the above patient-level data only.

All costs are reported in Sterling (£) rounded to the nearest whole £.

Statistical analysis. Variables were tested for normality using the Shapiro-Wilk test, following which comparisons were performed using either the Mann Whitney *U* or the Kruskal-Wallis tests. Survival data pertaining to AFS and overall survival were calculated using the Kaplan-Meier method, and groups were compared using the log rank statistic.

The analyses were performed using Jamovi version 1.0.8.0; a graphical user interface based on the R Statistical Package version 3.6.1 (The R Foundation for Statistical Computing, 2019). Graphical representations were produced using Prism version 8.3.0, GraphPad 2019.

RESULTS

From the period of June 1, 2014 to October 1, 2016, 259 patients were entered into the BASIL-PCS (all-comers with CLTI). From this cohort, 60 patients were selected for analysis (20 IP BS, 20 IP BET, 20 MLLA), which represented 23.2% of the total cohort.

Table I displays the demographics of the populations studied. All three groups were similar in terms of comorbidity profile, smoking status, obesity, mobility, clinical status, hemodynamic assessment, and WIFi clinical grade. More patients who underwent MLLA had undergone previous contralateral limb, above-ankle amputation in the past compared with the other two groups.

Procedural details for IP BS and BET can be found in Tables II and III, respectively. The majority of bypass patients underwent VB, with only one patient requiring a composite graft (reversed arm vein and PTFE). All grafts were successfully completed at the time of surgery with no immediate failures. All 20 BS cases were completed under general anesthesia. One patient in the BS group had a prolonged admission of 127 days and was a clear outlier. Their admission was complicated by significant distal calf wound dehiscence, thrombosis of arteriovenous fistulae for renal dialysis access, and urinary tract sepsis requiring admission to a higher level of care. The patient unfortunately died from sepsis during this hospital episode.

Reinterventions were numerous in all cohorts. In the IP BS group, three patients underwent revision surgery to the graft and/or wounds during the index admission. One patient had debridement of an infected groin wound (Clavien-Dindo IIIb). One graft thrombosed within 24 hours of surgery and was revised (Clavien-Dindo IIIb). One patient underwent below-knee amputation (BKA) in the same admission following graft failure with no other options for revascularization. In the 12 months following surgery, one patient underwent bilateral above-knee amputations for non-salvageable CLTI. One patient had an inflow angioplasty above the bypass graft for native artery disease. Another two patients had an outpatient angioplasty of a significant graft stenosis identified by duplex ultrasound surveillance. Two patients had infrainguinal endovascular treatment in the contralateral limb within 12 months of surgery. In total, four patients (20%) underwent repeated revascularization in the index limb during the study period.

All BET cases were performed by a consultant interventional radiologist using local anesthesia. As is standard

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Table I. Baseline demographics

Measure	Infra-popliteal bypass (n = 20)	Infra-popliteal best endovascular treatment (n = 20)	Major lower limb amputation (n = 20)	P
Male sex	15 (75)	14 (70)	12 (60)	.6
Age, years	74.21 ± 10.4	77.5 ± 10.9	77.1 ± 11.9	.6
Medical history				
Chronic kidney disease (eGFR <60 mL/min/kg)	6 (30)	9 (45)	8 (40)	.6
Dialysis dependence	1 (5)	2 (10)	2 (10)	.5
Stroke/TIA	3 (15)	3 (15)	4 (20)	.9
Myocardial infarction	6 (30)	4 (20)	4 (20)	.7
Angina	5 (25)	4 (20)	3 (15)	.7
Coronary artery bypass grafting	6 (30)	3 (15)	2 (10)	.2
Percutaneous coronary intervention	3 (15)	3 (15)	0 (-)	.2
Diabetes	9 (45)	12 (60)	11 (55)	.5
Insulin dependence	3/9 (33.3)	7/12 (58.3)	8/11 (72.7)	.5
Smoking status				.2
Current	7 (35)	2 (10)	5 (25)	
Ex	9 (45)	11 (55)	7 (35)	
Never	4 (20)	7 (35)	8 (40)	
Obesity (body mass index >30)	1 (5)	3 (15)	3 (15)	.5
Mobility				.2
Independent	7 (35)	3 (15)	1 (5)	
Walks with aides	12 (60)	16 (80)	10 (50)	
Wheelchair bound	1 (5)	2 (10)	7 (35)	
Bed bound	0 (–)	0 (–)	2 (10)	
Clinical status				
Rest pain	15 (75)	15 (75)	12 (60)	.5
Tissue loss	16 (80)	18 (90)	17 (85)	.7
Both	15 (75)	15 (75)	9 (45)	.4
Distribution of tissue loss				
Hallux	10/16 (62.5)	6/15 (40)	4/17 (23.5)	.1
Other toes	1/16 (6.3)	10/15 (66.6)	5/17 (29.4)	.006
Forefoot	1/16 (6.3)	2/15 (13.3)	5/17 (29.4)	.1
Hindfoot	2/16 (12.5)	0 (-)	3/17 (17.6)	.2
Ankle	2/16 (12.5)	2/15 (13.3)	2/17 (11.8)	1.0
Above ankle	2/16 (12.5)	3/15 (20)	6/17 (35.3)	.2
Medical therapy				
Aspirin	14 (70)	11 (55)	13 (65)	.9
Clopidogrel	5 (25)	5 (20)	6 (30)	.8
Other antiplatelet agent	4 (20)	0 (–)	0 (–)	.07
Cholesterol reducing agent	15 (75)	10 (50)	14 (70)	.5
Anti-hypertensive agent	16 (80)	14 (70)	14 (70)	.7
Warfarin	0 (–)	5 (20)	6 (30)	.02
Direct oral anticoagulant	0 (–)	1 (5)	0 (–)	.1
Considered best medical therapy	14 (70)	10 (50)	13 (65)	.8
Previous intervention				
Surgical (ipsilateral)	3 (15)	5 (25)	6 (30)	.2
Endovascular (ipsilateral)	5 (25)	2 (10)	4 (20)	.9

Table I. Continued.

Measure	Infra-popliteal bypass (n = 20)	Infra-popliteal best endovascular treatment (n = 20)	Major lower limb amputation (n = 20)	P
Minor amputation (ipsilateral)	2 (10)	3 (15)	2 (10)	.8
Major amputation (contralateral)	0 (-)	1 (5)	3 (15)	.02
APBI				.5
Symptomatic leg				
Not done	2 (10)	1 (5)	5 (25)	
Recorded	18 (90)	19 (95)	15 (75)	
Incompressible	1 (5)	6 (30)	2 (10)	
Unrecordable (no foot signal)	7 (35)	3 (15)	7 (35)	
Median ABPI (IQR)	0.38 (0.42-0.54)	0.49 (0.38-0.61)	0.48 (0.4-0.75)	
WIFi scores				.5
WIFi completion	19 (95)	19 (95)	17 (85)	
Total WIFi clinical grade (perceived risk of limb loss)				
Grade 1: very low	2/19 (10.5)	4/19 (21.0)	0 (—)	
Grade 2: low	6/19 (31.6)	7/19 (36.8)	6/17 (35.3)	
Grade 3: moderate	7/19 (36.8)	4/19 (21.0)	5/17 (29.4)	
Grade 4: high	4/19 (21.0)	1/19 (5.3)	6/17 (35.5)	

ABPI, Ankle brachial pressure index; *eGFR*, estimated glomular filtration rate; *IQR*, interquartile range; *TIA*, transient ischemic attack; *WIFi*, Wound Ischemia Foot infection.
Data are presented as number (%), mean ± standard deviation, or median (IQR).

practice in the UK, most (90%) had intervention to a single tibial vessel, which is usually the least diseased artery. A paclitaxel drug-coated balloon was used in one case. In two cases, it was not possible to cross the target IP lesion. One patient was discharged home for conservative treatment but was readmitted 2 months later and underwent a BKA. The patient unfortunately died 1 month following this of sepsis secondary to BKA wound ischemia. The other patient had rest pain only and had successful superficial femoral artery angioplasty but reestablishment of inline flow via the anterior tibial was unsuccessful. Treatment of the superficial femoral artery was sufficient to allow the patients management to continue conservatively until the patient's death in the community 3 years later. No bail-out bare metal stents were used in the endovascular cohort. Table III details the vessels treated and technical success rates of the primary interventions only. Subsequent reinterventions were not included.

Foot debridements were numerous in the BET cohort. Ten debridements were performed on eight patients. Eight of these were considered as primary debridement to remove infected or necrotic tissue following successful IP angioplasty. Two patients returned to theater for further debridement following a failure to heal, both as inpatients. A further patient had an above-knee amputation within 12 months in the index limb. Three patients (15%) had repeat infrainguinal endovascular treatment in the index limb during the study period.

There were no differences in AFS at 12 months (IP BS, 75% vs IP BET, 65%; hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.28-2.74; log rank $P = .82$) in those undergoing an attempt at revascularization (Fig 1).

The majority of MLLA (85%) were performed under general anesthesia. Three cases were completed under regional anesthesia with sedation. There was no significant difference in the total time or HR procedural costs between those undergoing transfemoral or transtibial amputations (Mann-Whitney *U*, not significant).

Patients undergoing MLLA had a longer median preintervention inpatient hospital stay (9 days; interquartile range [IQR], 3-21 days) than those undergoing BS (5 days; IQR, 1-9 days) or BET (2 days; IQR, 0-7 days) (Kruskal-Wallis, $P = .008$). Time to intervention was zero for four patients in the BS group and eight patients in the BET group who attended for a planned, semi-urgent intervention following outpatient assessment and management. Two of the BET patients were discharged from hospital on the day of intervention; a further three were discharged the following day. The remaining three patients had prolonged stays, requiring inpatient surgical management of tissue loss. In the MLLA group, only one patient was admitted on the day of surgery.

There were no significant differences in OS out to 12 months (log rank $P = .69$) (Fig 2), although OS was somewhat better in those undergoing IP BS (IP BS, 80%; IP BET, 75%; MLLA, 65%). Deaths in the MLLA group

Table II. Bypass treatment details

N = 20	No. (%)
Conduit	
Reversed vein	17 (85)
Non-reversed vein	3 (15)
Leg vein	18 (90)
Arm vein	2 (10)
Composite	1 (5)
Proximal anastomosis	
Common femoral artery	13 (65)
Superficial femoral artery	0 (–)
Profunda femoris artery	1 (5)
Above-knee popliteal artery	0 (–)
Below-knee popliteal artery	6 (30)
Distal anastomosis	
Tibioperoneal trunk	3 (15)
Posterior tibial artery 1/3	2 (10)
Posterior tibial artery 2/3	2 (10)
Posterior tibial artery 3/3	5 (25)
Peroneal artery 1/3	2 (10)
Peroneal artery 2/3	0 (–)
Peroneal artery 3/3	1 (5)
Anterior tibial artery 1/3	2 (10)
Anterior tibial artery 2/3	2 (10)
Anterior tibial artery 3/3	1 (5)
Dorsalis pedis	0 (–)

Table III. Endovascular treatment details

N = 20	No. (%)
Arteries treated[a]	
Superficial femoral	4 (20)
Above-knee popliteal	0 (–)
Below-knee popliteal	6 (30)
Tibio-peroneal trunk	3 (15)
Posterior tibial	6 (30)
Peroneal	7 (35)
Anterior tibial	8 (40)
Dorsalis pedis	0 (–)
Attempted number of tibial vessel recanalizations	
1 vessel	18 (90)
2 vessels	2 (10)
3 vessels	0 (–)
Type of disease treated	
Occlusive	14 (70)
Stenotic	5 (25)
Combination	1 (5)
PBA and stent use	
PBA only	19 (95)
PBA + bail-out BMS	0 (–)
Drug-coated balloon	1 (5)
Technical failure	2 (10)

BMS, Bare metal stent; *PBA*, percutaneous balloon angioplasty.
[a]Some patients had multiple vessels treated.

were caused by sepsis (2/20), cardiac arrest (2/20), "old age" (1/20), and unknown (2/20, community deaths unrecorded in hospital). In the IP BS group, mortality was caused by congestive cardiac failure (2/20), mesenteric ischemia (1/20), and unknown (1/20, community deaths unrecorded in hospital). Finally, in the IP BET group, deaths were due to sepsis (3/20) and unknown (2/20, community deaths unrecorded in hospital).

Procedural HR costs were significantly greater for IP BS than for IP BET or MLLA due to the longer procedural duration and the greater staff requirements, especially where two consultant surgeons were present[15] (Table IV). Fig 3 shows the spread of HR costs for the three primary interventions. The range of costs for those undergoing BS was much greater than it was for BET or MLLA, largely due to the more variable number of staff and time required to complete each case.

BS was the most intensive in terms of HR requirement. Four cases (20%) required the presence of two consultant surgeons. Consultant surgeon time is the most expensive at £108 p/h, trainee surgeon time is somewhat more variable (£24-£105 p/h, depending on grade). Having two junior level surgeons in theater for a case is still more likely to be less expensive than one consultant surgeon, given that very few non-consultant grade surgeons attract the higher tariff pay in the UK. If a single consultant surgeon was operating, they were accompanied by two or more junior surgeons for the majority of the operating time (13 cases; 65%). A consultant anesthetist was present in all 20 BS cases.

The HR requirements for BET were less variable. All cases were performed by one consultant interventional radiologist. A single training doctor of more junior grade was present for only 35% of cases. MLLA was most commonly performed by surgeons of non-consultant grade. A consultant surgeon was present in only four cases (20%). A consultant anesthetist was present in theater for all but one MLLA (95%).

Following their index intervention, patients undergoing BET spent less time in hospital (median, 1 day; IQR, 1-5 days) than those who received BS (median, 8 days; IQR, 4-17 days) or who required MLLA (median, 17 days; IQR, 11-28 days), (Kruskal-Wallis, $P < .001$).

Calculated in-hospital costs were significantly greater for MLLA than for either IP BS or IP BET, mainly due to increase length of the index hospital admission (Table IV, Fig 4).

There were no significant differences in readmissions, days spent in hospital, or outpatient appointments in the 12 months following discharge from the index admission (Table V), although these longer-term hospital costs

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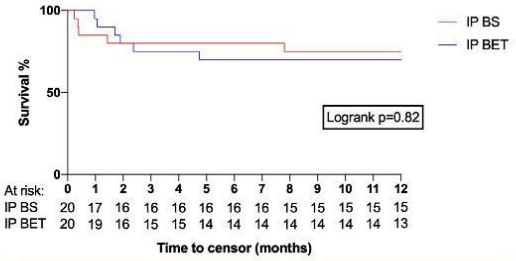


Fig 1. Amputation-free survival (AFS) associated with infra-popliteal (*IP*) bypass surgery (*BS*) and best endovascular treatment (*BET*).

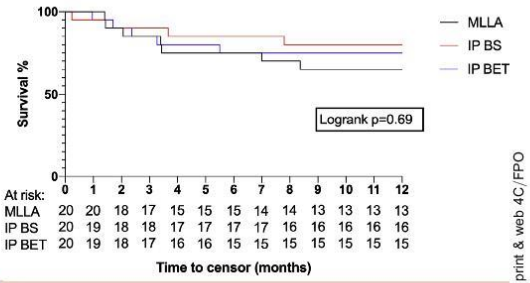


Fig 2. Overall survival associated with major lower limb amputation (*MLLA*), infra-popliteal (*IP*) bypass surgery (*BS*), and best endovascular treatment (*BET*).

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still differed significantly (MLLA £26,327; 95% CI, £17,653-£30,458 vs BS £20,401; 95% CI, £12,071-£23,926 vs BET £12,298; 95% CI, £6961-£15,439; $P < .001$, Kruskal-Wallis) (Fig 5). Although there were no differences in the cost of in-hospital care for patients undergoing MLLA compared with those undergoing IP BS, this does not include the considerable costs associated with ongoing community care, rehabilitation, and limb fitting.

DISCUSSION

The present study has found that, over a 12-month time horizon, IP BS is more expensive than IP BET or MLLA in terms of procedural HR costs due to the greater requirements for time and staff. This accords with other published data.[18] This was largely due to the presence of more consultant grade staff (at least two, one surgeon and one anesthetist) and assistants required for BS. The range of HR costs of BS was greater than for the other two interventions, probably due to variations in conduit use (arm vein, for example) and the location of the distal anastomosis. BS by nature is less predictable, and each case presents its own unique challenges. MLLA is a much more predictable operation.

Although from a technical perspective, BET can also be unpredictable, the HR costs were more tightly grouped. All cases were performed under local anesthesia, by a single consultant interventional radiologist without the requirement of an anesthetist. Following manual compression, or use of closure device, and adequate hemostasis, patients returned directly to the vascular ward without the need for the use of a recovery area. These factors largely explain the lower HR costs for BET.

BET was also the least expensive intervention in terms of in-hospital costs, which is perhaps unsurprising, given that BET is generally quicker to perform and requires less recovery in-hospital. Eight patients (8/20; 40%) underwent planned, semi-elective therapy, which was a much higher proportion than those undergoing MLLA or BS.

Patients undergoing MLLA tended to have a prolonged index admission. Moreover, timely discharge to "step-down" facilities for ongoing care would have reduced the hospital costs associated with the index admission. Also, the lead time from admission to MLLA was relatively long (median, 9 days) largely due to prior attempts at limb salvage, debridement, or drainage of sepsis; or an initial unwillingness on the part of the patient to accept MLLA.

The index in-hospital admission costs for all three procedures are tightly grouped (Fig 2) except one outlier who underwent BS. This patient had a protracted stay in hospital following a femoro-peroneal bypass with complicated wound sepsis (groin) that required debridement, negative pressure therapy, and an intensive care stay with acute renal failure.

Ongoing hospital-based care in terms of outpatient appointments, readmissions, and days spent in hospital in the 12 months following discharge after the index intervention were non-significantly different. When comparing the sum of in-hospital costs during the index admission and hospital-based care over the following 12 months, costs were greatest for those undergoing MLLA and BS. This was due to the relatively expensive index episodes.

We opted not to individually cost for devices and equipment, based on the complexities of health care purchasing in the UK NHS. Each individual NHS hospital trust has contracts with different device manufacturers that are often based on the volume and frequency of use as well as consignment stock. Each hospital trust has its own financial agreement with manufacturers. The financial details of these agreements are usually not disclosed. For these reasons, the cost of devices in our unit may be very different from other hospitals with different device preference and frequencies of use.

There were no pedal bypasses in the IP BS cohort. In recent years, our colleagues have increasingly adopted an endovascular-first revascularization strategy in patients presenting with CLTI. In the period from which the current patients were selected (June 2014 to September 2016), 259 patients were admitted to HEFT

Table IV. Procedural human resource costs of *MLLA*, *IP BS*, and *IP PBA*

	MLLA (n = 20)	IP BS (n = 20)	IP PBA (n = 20)	*P*
Mean (IQR) time, minutes				
Time from arrival in theatre to start of anesthetic	13 (10-20)	9 (7-12)	N/A	
Anesthetic time	39 (25-46)	44 (29-51)	N/A	
Operative time	85 (75-103)	241 (197-292)	58 (44-68)	
Recovery time	48 (41-93)	83 (65-127)	N/A	
Total time	194 (180-233)	320 (283-432)	58 (44-68)	<.001
Median (IQR) cost, UK£				
Surgeon or interventional radiologist	134 (38-287)	798 (151-2158)	113 (63-333)	<.001
Anesthetist	309 (194-529)	624 (189-1015)	N/A	<.001
Nursing staff	506 (339-1014)	708 (341-1359)	144 (107-174)	<.001
Operating department practitioner	134 (97-396)	220 (95-512)	N/A	.003
Radiographer	N/A	N/A	53 (38-77)	N/A
Median total	1130 (720-1820)	2551 (776-4083)	329 (161-962)	<.001

BS, Bypass surgery; *IP*, infra-popliteal; *IQR*, interquartile range; *MLLA*, major lower limb amputation; *N/A*, not applicable; *PBA*, plain balloon angioplasty; *UK*, United Kingdom.

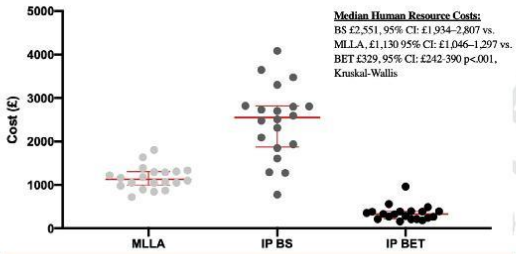


Fig 3. Procedural human resource (HR) costs associated with major lower limb amputation (*MLLA*), infra-popliteal (*IP*) bypass surgery (*BS*), and best endovascular treatment (*BET*). *Red bars* denote median and interquartile range (IQR). *CI*, Confidence interval.

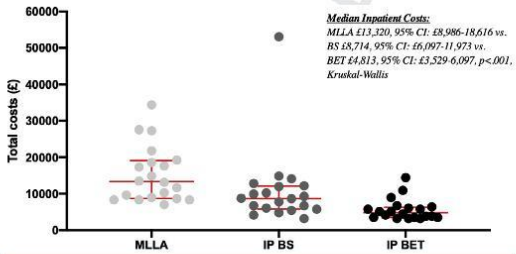


Fig 4. In-hospital costs during index admission for major lower limb amputation (*MLLA*), infra-popliteal (*IP*) bypass surgery (*BS*), and best endovascular treatment (*BET*). *Red bars* denote median and interquartile range (IQR). *CI*, Confidence interval.

UHB with CLTI as an emergency (for inpatient care). During this time period, only one popliteal to pedal (dorsalis pedis artery) bypass was performed.

Patients undergoing IP BS had longer delays to treatment than those undergoing IP BET. This is likely to be the case in most, if not all, UK vascular units. Patient who require IP BS often require a much more extensive pre-procedural workup in terms of anesthetic review, further investigations to delineate fitness for treatment, and often more investigations (vein map, computed tomography angiography, arterial duplex, digital subtraction angiography) compared with those undergoing IP BET. In addition, it can be difficult to access sufficient operating theater time for often prolonged emergency surgery. Again, this is a common problem across the NHS.

Costs need to be weighed against patient outcomes and, in particular, data on health-related quality of life, so that a cost-utility analysis can be used to compare cost-effectiveness of different treatment strategies. In the UK, The National Institute of Health and Care Excellence use cost per quality-adjusted life-year (QALY) as a marker of value, with a current willingness to pay threshold set nationally at £20,000 per QALY.[18] A recent systematic review into the cost-effectiveness of a BET vs BS strategy for patients with CLTI secondary to infrainguinal disease reported that BASIL-1 was the only randomized controlled trial (RCT) for which health economic data were available.[19] The Veterans Association study group concluded that significant, modern evidence was severely lacking to inform health care providers and that future ongoing RCTs are required to provide this (BASIL-2,[20] BEST-CLI[21]).

Human resource costs are notoriously difficult to estimate; the PSSRU[15] document that we used to calculate such costs is a standardized format based on average basic salaries. This does not include any uplifts in pay for extra activity, such as teaching or managerial roles

Table V. Comparison of resource usage and costs associated with *MLLA*, *IP BS*, and *BET*

Median (IQR)	MLLA (n = 20)	BS (n = 20)	BET (n = 20)	P
Days from admission to intervention	9 (3-19)	5 (1-8)	2 (0-6)	<.001
Days spent in hospital following intervention	17 (11-28)	8 (4-7)	1 (1-5)	<.001
Inpatient bed days during index admission	30 (18-45)	11 (7-23)	5 (1-9)	<.001
Index admission costs, £	13,320 (8745-19,098)	8714 (5856-12,140)	4813 (3529-6338)	<.001
Hospital admissions following index admissions	1 (0-2)	1.5 (0.75-2)	1 (0-2)	NS
Days spent in hospital in the 12 months following discharge from the index admission	7 (0-20)	15 (2.5-24.3)	7.5 (0-13.3)	NS
Outpatient appointments following discharge from the index admission	2 (0-6.25)	4 (2.5-7.25)	2 (1-3.25)	NS
The sum of in-hospital costs over 12 months (from index admission to 12 months after discharge from index admission), £	26,327 (17,447-31,973)	20,401 (10,903-26,266)	12,298 (5429-16,029)	<.001

BET, Best endovascular treatment; *BS*, bypass surgery; *IP*, infra-popliteal; *IQR*, interquartile range; *MLLA*, major lower limb amputation; *NS*, not significant.

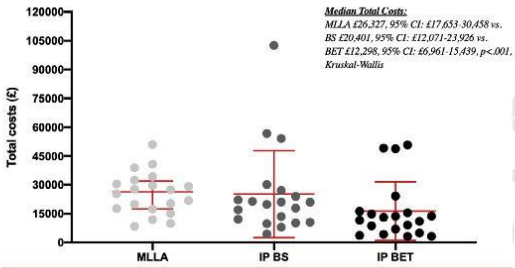


Fig 5. The sum of in-hospital costs from index admission to 12 months after discharge for index admission for major lower limb amputation (*MLLA*), infra-popliteal (*IP*) bypass surgery (*BS*), and best endovascular treatment (*BET*). *Red bars* denote median and interquartile range (IQR). *CI*, Confidence interval.

or service awards. Although PSSRU HR costs may have been an underestimate, it is the best data source available.

Limitations. The current study estimates costs over a relatively short, 12-month time horizon and so does not include the costs of later readmissions and reinterventions, rehabilitation, limb fitting, and ongoing social care, either at home or in a residential institution.

Rehabilitation services are completely separate from the hospital. Following discharge from hospital, patients with MLLA are usually seen in the outpatient department at around 6 weeks to ensure adequate wound healing. If there are no concerns, they are usually discharged from the vascular service.

Although NHS hospitals are likely to have varying salary and estates costs, we cannot comment formally on the generalizability of our data to other UK vascular units.

Bearing this in mind, and the dearth of evidence in the literature regarding the true costs of managing CLTI, further large, multicenter studies are clearly required.

Our aim was to assess the costs of caring for patients with CLTI during their index hospital admission and over the following 12 months. The study was not designed to, and indeed cannot, address the question of the relative long-term clinical and cost-effectiveness of different treatment strategies for CLTI. Only large RCTs such as BASIL-2 and BASIL-3 in the UK and BEST-CLI in the U.S. can address this question.

In conclusion, over a 12-month horizon, in terms of calculated procedural HR and in-hospital costs, both IP VB and MLLA are more expensive than IP PBA. Although out to 12 months after discharge from the index admission, the difference in overall hospital costs reduces, it remains significant. These economic data together with QALY data from BASIL-2 will help inform the calculation of incremental cost-effectiveness ratios for different CLTI management strategies.

AUTHOR CONTRIBUTIONS

Conception and design: MP, LA, AB
Analysis and interpretation: MP, LA, LM, LK, GB, AB
Data collection: MP, HD, LM, LK, GB
Writing the article: MP
Critical revision of the article: MP, LA, HD, LM, LK, GB, AB
Final approval of the article: MP, LA, HD, LM, LK, GB, AB
Statistical analysis: MP
Obtained funding: Not applicable
Overall responsibility: MP

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Submitted Aug 10, 2020; accepted Jul 23, 2021.

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